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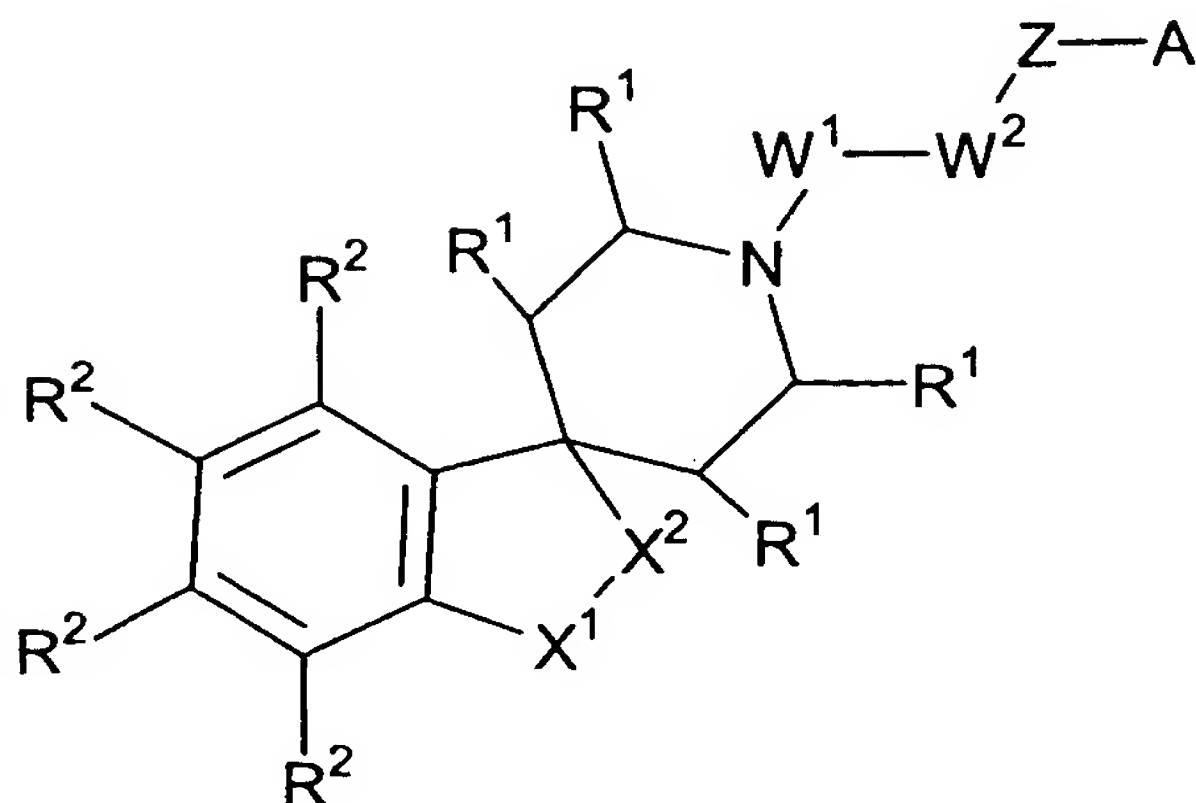
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(54) Title: SPIROPIPERIDINE COMPOUNDS AS LIGANDS FOR ORL-1 RECEPTOR



(57) Abstract: A compound of the formula (I) or a salt, prodrug or solvate thereof, wherein R¹ and R² groups are all hydrogen; A is a benzofused azahetero ring; W¹-W² is CH₂-CH₂; X¹-X¹ is CH₂-CH₂; and Z is methylene or carbonyl; or the like, is a ligand for ORL1-receptor and are useful for treating or preventing pain, a CNS disorder or the like in mammalian subjects.

(I)

SPIROPIPERIDINE COMPOUNDS AS LIGANDS
FOR ORL-1 RECEPTOR

TECHNICAL FIELD

5 This invention relates to substituted spiropiperidine compounds and their salts, prodrugs and solvates, and a medical use thereof. Also, this invention relates to a pharmaceutical composition comprising said compound, or its salt, prodrug or solvate. The compounds of this invention have binding affinity for ORL-1 receptor. In particular, compounds of this invention have selective antagonist activity for said
10 receptor. The compounds of this invention are useful in treating or preventing disorders or medical conditions selected from pain, a CNS disorder and the like, which is mediated by said receptor and its endogenous ligand.

BACKGROUND ART

15 Three types of opioid receptors, μ (mu), δ (delta) and κ (kappa) have been identified. These receptors may be indicated with combinations of OP (abbreviation for Opioid Peptides) and numeric subscripts as suggested by the International Union of Pharmacology (IUPHAR). Namely, OP_1 , OP_2 and OP_3 respectively correspond to δ -, κ - and μ -receptors. It has been found out that they belong to G-protein-coupled
20 receptors and distribute in the central nervous system (CNS), peripheries and organs in a mammal. As ligands for the receptors, endogenous and synthetic opioids are known. It is believed that an endogenous opioid peptide produces their effects through an interaction with the major classes of opioid receptors. For example, endorphins have been purified as endogenous opioid peptides and bind to both δ - and
25 μ -receptors. Morphine is a well-known non-peptide opioid analgesic and has binding affinity mainly for μ -receptor. Opiates have been widely used as pharmacological agents, but drugs such as morphine and heroin induce some side effects such as drug addiction and euphoria.

 Further, Meunier *et al.* reported isolation of a seventeen-amino-acid-long
30 peptide from rat brain as an endogenous ligand for an orphan opioid receptor (Nature, Vol. 337, pp. 532-535, October 12, 1995). The receptor is known as "opioid receptor-like 1 (abbreviated as ORL1-receptor)" which is believed to be almost as

homologous to any of μ -, δ - and κ -receptors. In the same report, the endogenous opioid ligand has been introduced as agonist for ORL-1 receptor and named as "nociceptine (abbreviated as NC)". Also, the same ligand was named as "orphanin FQ (abbreviated as OFQ or oFQ)" by Reinscheid *et al.* (Science, Vol. 270, pp. 792-794, 1995). This receptor may be indicated as OP_4 in line with a recommendation by IUPHAR in 1998 (British Journal of Pharmacology, Vol. 129, pp. 1261-1283, 2000).

Opioids and their affinity for these receptors have been researched *in-vitro* and *in-vivo*. It is possible to date to test whether an opioid has agonist or antagonist properties or a combination of both on the receptors.

Use of a synthetic ORL1-receptor ligand or antagonist as an analgesic is disclosed in WO 00/27815 (Smithkline Beecham Spa) or WO 99/48492 (Japan Tobacco Inc.).

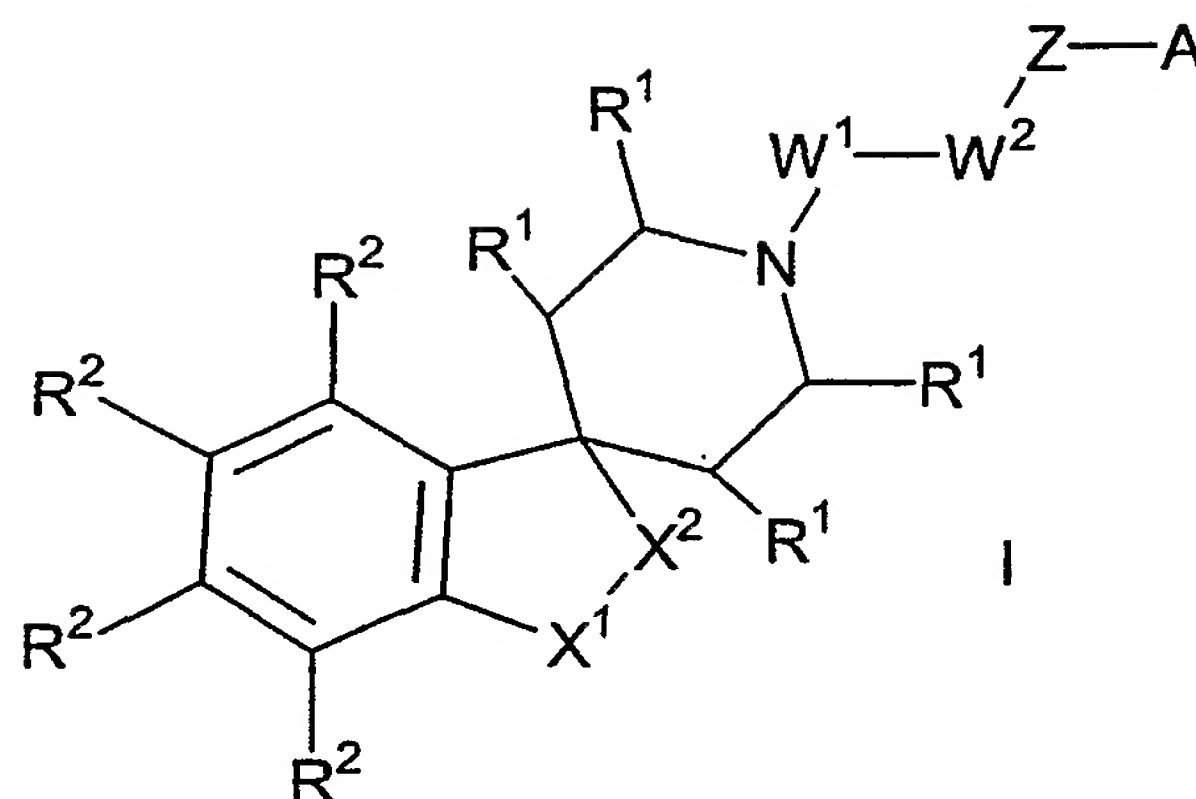
Use of a synthetic ORL1-receptor antagonist for treating a CNS disorder is disclosed in WO 00/27815 (Smithkline Beecham Spa), WO 99/29696 (F. Hoffmann-La Roche AG) or British Journal of Pharmacology, Vol. 129, pp. 1261-1283, 2000 by G. Calo *et al.*

Banyu's WO 98/54168, WO 00/31061, WO 00/34280 and Japanese Patent Publication Kokai 2000-169476 disclose use of a synthetic ORL1-receptor ligand or antagonist as an analgesic or for treating a CNS disorder.

Schering's WO 01/07051 discloses use of a synthetic ORL-1 agonist in treating cough.

BRIEF DISCLOSURE OF THE INVENTION

The present invention provides a compound of the following formula:



or pharmaceutically acceptable salts thereof, wherein

each R^1 is independently selected from hydrogen and (C_1-C_6) alkyl optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, $[(C_1-C_6)\text{alkyl}]-C(=O)-$, (C_1-C_6) alkoxy, $[(C_1-C_6)\text{alkoxy}]-C(=O)-$, $R^{a1}R^{a2}N-$ and $R^{a3}R^{a4}N-C(=O)-$, wherein R^{a1} , R^{a2} , R^{a3} and R^{a4} are independently selected from hydrogen, (C_1-C_6) alkyl, $[(C_1-C_6)\text{alkyl}]-C(=O)-$, $[(C_1-C_6)\text{alkoxy}]-C(=O)-$ and $[(C_1-C_6)\text{alkyl}]-SO_2-$; or

two R^1 groups taken together form $-CH_2-$ or $-(CH_2)_2-$ and the remaining R^1 groups are defined as above;

each R^2 is independently selected from

hydrogen; halo; hydroxy; (C_1-C_6) alkyl optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, $[(C_1-C_6)\text{alkyl}]-C(=O)-$, (C_1-C_6) alkoxy, $[(C_1-C_6)\text{alkoxy}]-C(=O)-$, $R^{a1}R^{a2}N-$ and $R^{a3}R^{a4}N-C(=O)-$, wherein R^{a1} , R^{a2} , R^{a3} and R^{a4} are independently selected from hydrogen, (C_1-C_6) alkyl, $[(C_1-C_6)\text{alkyl}]-C(=O)-$, $[(C_1-C_6)\text{alkoxy}]-C(=O)-$ and $[(C_1-C_6)\text{alkyl}]-SO_2-$; (C_1-C_6) alkoxy optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, $[(C_1-C_6)\text{alkyl}]-C(=O)-$, (C_1-C_6) alkoxy, $[(C_1-C_6)\text{alkoxy}]-C(=O)-$, $R^{a5}R^{a6}N-$ and $R^{a7}R^{a8}N-C(=O)-$, wherein R^{a5} , R^{a6} , R^{a7} and R^{a8} are independently selected from hydrogen, (C_1-C_6) alkyl, $[(C_1-C_6)\text{alkyl}]-C(=O)-$, $[(C_1-C_6)\text{alkoxy}]-C(=O)-$ and $[(C_1-C_6)\text{alkyl}]-SO_2-$; non-, mono- and di-substituted amino wherein the substituents are independently selected from (C_1-C_6) alkyl, $[(C_1-C_6)\text{alkyl}]-C(=O)-$, $[(C_1-C_6)\text{alkoxy}]-C(=O)-$ and $[(C_1-C_6)\text{alkyl}]-SO_2-$; aryl selected from phenyl and naphthyl; and four- to eight-membered heterocyclyl containing one to four hetero atoms in the ring independently selected from

nitrogen, oxygen and sulfur;

X^1 and X^2 are independently selected from

(CH₂)_{n1} wherein n1 is an integer selected from 1, 2 and 3; C[(C₁-C₆)alkyl]; C-OH; O; NH; S; C(=O); SO₂; NR^{X1}; N-C(=O)R^{X2}; N-C(=O)OR^{X3}; and N-C(=O)NR^{X4}R^{X5}; wherein R^{X1}, R^{X2}, R^{X3}, R^{X4} and R^{X5} are independently (C₁-C₆)alkyl optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, [(C₁-C₆)alkyl]-C(=O)-, (C₁-C₆)alkoxy, [(C₁-C₆)alkoxy]-C(=O)-, R^{a1}R^{a2}N- and R^{a3}R^{a4}N-C(=O)-, wherein R^{a1}, R^{a2}, R^{a3} and R^{a4} are independently selected from hydrogen, (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-; or

X^1 and X^2 taken together form CH=CH;

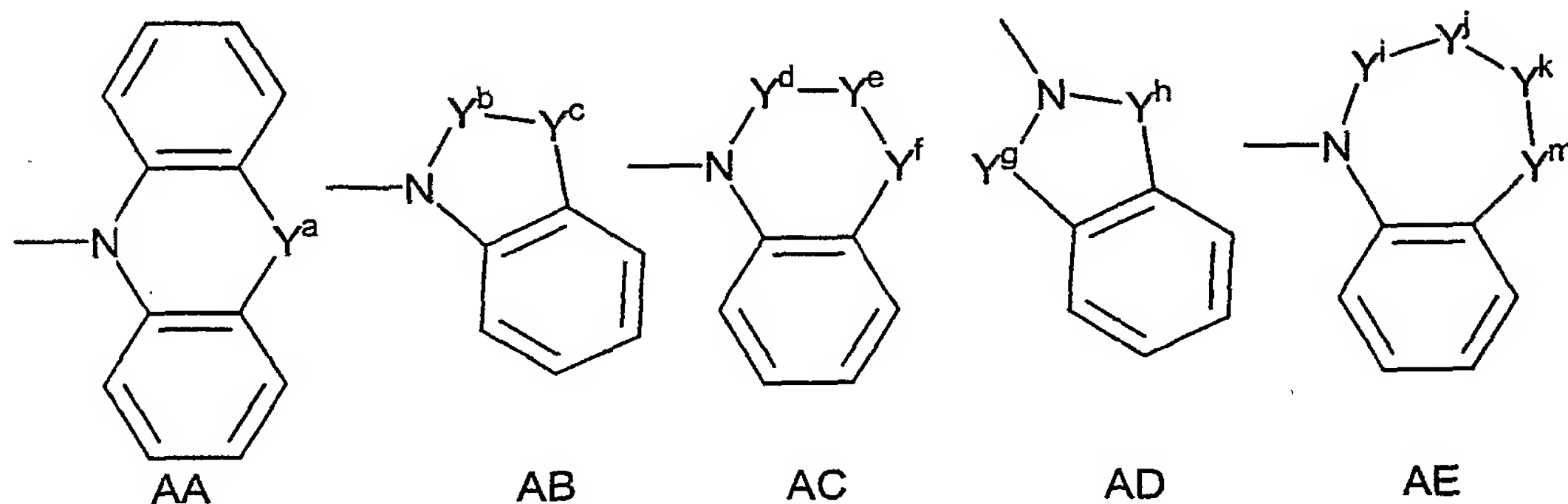
W¹ and W² are independently selected from CR^{W1}R^{W2}, wherein

R^{W1} and R^{W2} are independently selected from hydrogen; halo; hydroxy; (C₁-C₆)alkyl optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, [(C₁-C₆)alkyl]-C(=O)-, (C₁-C₆)alkoxy, [(C₁-C₆)alkoxy]-C(=O)-, R^{a1}R^{a2}N- and R^{a3}R^{a4}N-C(=O)-, wherein R^{a1}, R^{a2}, R^{a3} and R^{a4} are independently selected from hydrogen, (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-; (C₁-C₆)alkoxy optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, [(C₁-C₆)alkyl]-C(=O)-, (C₁-C₆)alkoxy, [(C₁-C₆)alkoxy]-C(=O)-, R^{a5}R^{a6}N- and R^{a7}R^{a8}N-C(=O)-, wherein R^{a5}, R^{a6}, R^{a7} and R^{a8} are independently selected from hydrogen, (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-;

C(=O)-[(C₁-C₆)alkyl] wherein said (C₁-C₆)alkyl is optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, [(C₁-C₆)alkyl]-C(=O)-, (C₁-C₆)alkoxy, [(C₁-C₆)alkoxy]-C(=O)-, R^{a1}R^{a2}N- and R^{a3}R^{a4}N-C(=O)-, wherein R^{a1}, R^{a2}, R^{a3} and R^{a4} are independently selected from hydrogen, (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-; C(=O)-NR^{W11}R^{W12} wherein R^{W11} and R^{W12} are independently selected from hydrogen and (C₁-C₆)alkyl optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, [(C₁-C₆)alkyl]-C(=O)-, (C₁-C₆)alkoxy, [(C₁-C₆)alkoxy]-C(=O)-, R^{a1}R^{a2}N- and

$R^{a3}R^{a4}N-C(=O)-$, wherein R^{a1} , R^{a2} , R^{a3} and R^{a4} are independently selected from hydrogen, $(C_1-C_6)alkyl$, $[(C_1-C_6)alkyl]-C(=O)-$, $[(C_1-C_6)alkoxy]-C(=O)-$ and $[(C_1-C_6)alkyl]-SO_2-$; $NR^{w13}R^{w14}$ wherein R^{w13} and R^{w14} are independently selected from hydrogen and $(C_1-C_6)alkyl$ optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, $[(C_1-C_6)alkyl]-C(=O)-$, $(C_1-C_6)alkoxy$, $[(C_1-C_6)alkoxy]-C(=O)-$, $R^{a1}R^{a2}N-$ and $R^{a3}R^{a4}N-C(=O)-$, wherein R^{a1} , R^{a2} , R^{a3} and R^{a4} are independently selected from hydrogen, $(C_1-C_6)alkyl$, $[(C_1-C_6)alkyl]-C(=O)-$, $[(C_1-C_6)alkoxy]-C(=O)-$ and $[(C_1-C_6)alkyl]-SO_2-$; aryl selected from phenyl and naphthyl; and four- to eight-membered heterocyclyl containing one to four hetero atoms independently selected from nitrogen, oxygen and sulfur;

A is selected from AA; AB; AC; AD and AE:



wherein

Y^a is selected from $(CH_2)_{n2}$ wherein $n2$ is an integer selected from 0, 1 and 2; $C(=O)$; NH ; O and S ;
 Y^b , Y^c , Y^d , Y^e , Y^f , Y^g , Y^h , Y^i , Y^j , Y^k and Y^m are independently selected from $C(=O)$; $CR^{Y1}R^{Y2}$; $CR^{Y3}[C(=O)R^{Y4}]$; $CR^{Y3}[NR^{Y5}C(=O)R^{Y4}]$; $CR^{Y3}[C(=O)NR^{Y6}R^{Y7}]$; $CR^{Y3}[NR^{Y6}R^{Y7}]$; O ; S ; SO_2 ; NH ; $N[(C_1-C_6)alkyl]$ wherein said $(C_1-C_6)alkyl$ is optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, $[(C_1-C_6)alkyl]-C(=O)-$, $(C_1-C_6)alkoxy$, $[(C_1-C_6)alkoxy]-C(=O)-$, $R^{a1}R^{a2}N-$ and $R^{a3}R^{a4}N-C(=O)-$, wherein R^{a1} , R^{a2} , R^{a3} and R^{a4} are independently selected from hydrogen, $(C_1-C_6)alkyl$, $[(C_1-C_6)alkyl]-C(=O)-$, $[(C_1-C_6)alkoxy]-C(=O)-$ and $[(C_1-C_6)alkyl]-SO_2-$; $N-(CH_2)_{n3}$ -heterocyclyl wherein $n3$ is an integer selected from 0, 1, 2 and 3, and said heterocyclyl contains from four to eight ring atoms one or two of which are independently selected from nitrogen,

oxygen and sulfur; $N-(CH_2)_{n4}$ -aryl wherein $n4$ is an integer selected from 0, 1, 2 and 3, and said aryl is selected from phenyl and naphthyl; and $N-(CH_2)_{n5}$ -heteroaryl wherein $n5$ is an integer selected from 0, 1, 2 and 3, and said heteroaryl is a five to ten membered aromatic heterocyclyl containing from one
 5 to four hetero atoms independently selected from nitrogen, oxygen and sulfur; or Y^b and Y^c taken together form a group selected from $CR^{Y81}=CR^{Y82}$; $CR^{Y83}=N$ and $N=N$; and Y^d , Y^e , Y^f , Y^g and Y^h are defined as above; wherein

R^{Y1} , R^{Y2} and R^{Y5} are independently selected from hydrogen; hydroxy; non-, mono- and di-substituted amino wherein the substituents are independently
 10 selected from (C_1-C_6) alkyl; $[(C_1-C_6)alkyl]-C(=O)-$; $[(C_1-C_6)alkoxy]-C(=O)-$; $[(C_1-C_6)alkyl]-SO_2-$; and four- to eight-membered heterocyclyl containing one to four hetero atoms independently selected from nitrogen, oxygen and sulfur, wherein said heterocyclyl is optionally substituted with one to three substituents independently selected from hydroxy, (C_1-C_6) alkyl, $NH_2-C(=O)-$,
 15 $[(C_1-C_6)alkyl]-NH-C(=O)-$, $[(C_1-C_6)alkyl]_2-N-C(=O)-$, and non-, mono- and di-substituted amino wherein the substituents are independently selected from (C_1-C_6) alkyl, $[(C_1-C_6)alkyl]-C(=O)-$, $[(C_1-C_6)alkoxy]-C(=O)-$ and $[(C_1-C_6)alkyl]-SO_2-$; (C_1-C_6) alkyl optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, $[(C_1-C_6)alkyl]-C(=O)-$, $(C_1-C_6)alkoxy$, $[(C_1-C_6)alkoxy]-C(=O)-$, $R^{a1}R^{a2}N-$ and $R^{a3}R^{a4}N-C(=O)-$, wherein R^{a1} , R^{a2} , R^{a3} and R^{a4} are independently selected from hydrogen, (C_1-C_6) alkyl, $[(C_1-C_6)alkyl]-C(=O)-$, $[(C_1-C_6)alkoxy]-C(=O)-$ and $[(C_1-C_6)alkyl]-SO_2-$; and $(C_1-C_6)alkoxy$ optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, $[(C_1-C_6)alkyl]-C(=O)-$, $(C_1-C_6)alkoxy$, $[(C_1-C_6)alkoxy]-C(=O)-$, $R^{a5}R^{a6}N-$ and $R^{a7}R^{a8}N-C(=O)-$, wherein R^{a5} , R^{a6} , R^{a7} and R^{a8} are independently selected from hydrogen, (C_1-C_6) alkyl, $[(C_1-C_6)alkyl]-C(=O)-$, $[(C_1-C_6)alkoxy]-C(=O)-$ and $[(C_1-C_6)alkyl]-SO_2-$; or
 20 R^{Y1} and R^{Y2} taken together with the carbon atom to which they are attached form spiropyrrolidinyl or spiropiperidinyl, both of which are optionally N-substituted with a substituent selected from (C_1-C_6) alkyl, $(C_1-C_6)alkyl-C(=O)-$, $[(C_1-C_6)alkyl]-C(=O)-(C_1-C_6)alkyl$ and aryl- $C(=O)-$ wherein aryl is selected
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from phenyl and naphthyl; and R^{Y5} is defined as above;

R^{Y3} is hydrogen;

R^{Y4} is selected from hydroxy; (C_1-C_6) alkyl optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, $[(C_1-C_6)alkyl]-C(=O)-$, $(C_1-C_6)alkoxy$, $[(C_1-C_6)alkoxy]-C(=O)-$, $R^{a1}R^{a2}N-$ and $R^{a3}R^{a4}N-C(=O)-$, wherein R^{a1} , R^{a2} , R^{a3} and R^{a4} are independently selected from hydrogen, $(C_1-C_6)alkyl$, $[(C_1-C_6)alkyl]-C(=O)-$, $[(C_1-C_6)alkoxy]-C(=O)-$ and $[(C_1-C_6)alkyl]-SO_2-$; and $(C_1-C_6)alkoxy$ optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, $[(C_1-C_6)alkyl]-C(=O)-$, $(C_1-C_6)alkoxy$, $[(C_1-C_6)alkoxy]-C(=O)-$, $R^{a5}R^{a6}N-$ and $R^{a7}R^{a8}N-C(=O)-$, wherein R^{a5} , R^{a6} , R^{a7} and R^{a8} are independently selected from hydrogen, $(C_1-C_6)alkyl$, $[(C_1-C_6)alkyl]-C(=O)-$, $[(C_1-C_6)alkoxy]-C(=O)-$ and $[(C_1-C_6)alkyl]-SO_2-$; and

R^{Y6} and R^{Y7} are independently selected from hydrogen; $(C_1-C_6)alkyl$ optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, $[(C_1-C_6)alkyl]-C(=O)-$, $(C_1-C_6)alkoxy$, $[(C_1-C_6)alkoxy]-C(=O)-$, $R^{a1}R^{a2}N-$ and $R^{a3}R^{a4}N-C(=O)-$, wherein R^{a1} , R^{a2} , R^{a3} and R^{a4} are independently selected from hydrogen, $(C_1-C_6)alkyl$, $[(C_1-C_6)alkyl]-C(=O)-$, $[(C_1-C_6)alkoxy]-C(=O)-$ and $[(C_1-C_6)alkyl]-SO_2-$; heterocyclyl- $(CH_2)_{n6}-$ wherein $n6$ is an integer selected from 0, 1, 2, 3 and 4 and said heterocyclyl is four to eight membered containing one to three hetero atoms independently selected from nitrogen, oxygen and sulfur, wherein said heterocyclyl is optionally substituted with one to three substituents independently selected from hydroxy; $(C_1-C_6)alkyl$; $NH_2-C(=O)-$; $(C_1-C_6)alkyl-NH-C(=O)-$; $[(C_1-C_6)alkyl]_2-N-C(=O)-$; and non-, mono- and di-substituted amino wherein the substituents are independently selected from $(C_1-C_6)alkyl$, $[(C_1-C_6)alkyl]-C(=O)-$, $[(C_1-C_6)alkoxy]-C(=O)-$ and $[(C_1-C_6)alkyl]-SO_2-$; and heteroaryl- $(CH_2)_{n7}-$ wherein $n7$ is an integer selected from 0, 1, 2, 3 and 4 and said heteroaryl is five to ten membered containing one to three hetero atoms independently selected from nitrogen, oxygen and sulfur, wherein said heteroaryl is optionally substituted with one to three substituents independently selected from hydroxy; $(C_1-C_6)alkyl$; $NH_2-C(=O)-$; $(C_1-C_6)alkyl-NH-C(=O)-$; $[(C_1-C_6)alkyl]_2-N-C(=O)-$;

and non-, mono- and di-substituted amino wherein the substituents are independently selected from (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-; or R^{Y6} and R^{Y7} taken together with the nitrogen atom to which they are attached form a four to eight heterocyclyl optionally containing, in addition to the nitrogen atom, one to two additional hetero atoms independently selected from nitrogen, oxygen and sulfur, and said heterocyclyl is optionally substituted with one substituent selected from hydroxy; (C₁-C₆)alkyl; NH₂-C(=O)-; (C₁-C₆)alkyl-NH-C(=O)-; [(C₁-C₆)alkyl]₂-N-C(=O)-; and non-, mono- and di-substituted amino wherein the substituents are independently selected from (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-;

R^{Y81}, R^{Y82} and R^{Y83} are independently selected from R^{Y811} and R^{Y812}C(=O)- wherein R^{Y811} and R^{Y812} are independently selected from hydrogen; hydroxy; (C₁-C₆)alkyl optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, [(C₁-C₆)alkyl]-C(=O)-, (C₁-C₆)alkoxy, [(C₁-C₆)alkoxy]-C(=O)-, R^{a1}R^{a2}N- and R^{a3}R^{a4}N-C(=O)-, wherein R^{a1}, R^{a2}, R^{a3} and R^{a4} are independently selected from hydrogen, (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-; and (C₁-C₆)alkoxy optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, [(C₁-C₆)alkyl]-C(=O)-, (C₁-C₆)alkoxy, [(C₁-C₆)alkoxy]-C(=O)-, R^{a5}R^{a6}N- and R^{a7}R^{a8}N-C(=O)-, wherein R^{a5}, R^{a6}, R^{a7} and R^{a8} are independently selected from hydrogen, (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-; and

said A is optionally substituted in the fused benzene rings with one to four substituents independently selected from halo; hydroxy; mercapto; phenyl; (C₁-C₆)alkyl optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, [(C₁-C₆)alkyl]-C(=O)-, (C₁-C₆)alkoxy, [(C₁-C₆)alkoxy]-C(=O)-, R^{a1}R^{a2}N- and R^{a3}R^{a4}N-C(=O)-, wherein R^{a1}, R^{a2}, R^{a3} and R^{a4} are independently selected from hydrogen, (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-; and (C₁-C₆)alkoxy optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, [(C₁-C₆)alkyl]-C(=O)-, (C₁-

C_6)alkoxy, $[(C_1-C_6)\text{alkoxy}]-C(=O)-$, $R^{a5}R^{a6}N-$ and $R^{a7}R^{a8}N-C(=O)-$, wherein R^{a5} , R^{a6} , R^{a7} and R^{a8} are independently selected from hydrogen, $(C_1-C_6)\text{alkyl}$, $[(C_1-C_6)\text{alkyl}]-C(=O)-$, $[(C_1-C_6)\text{alkoxy}]-C(=O)-$ and $[(C_1-C_6)\text{alkyl}]-SO_2-$; and

Z is selected from $C(=O)$; $(CH_2)_{n8}$ wherein $n8$ is an integer selected from 0, 1 and 2;

5 and CHR^{Z1} wherein R^{Z1} is selected from carboxy; $(C_1-C_6)\text{alkoxy}-C(=O)-$; non-, mono- and di-substituted amino wherein the substituents are independently selected from $(C_1-C_6)\text{alkyl}$, $[(C_1-C_6)\text{alkyl}]-C(=O)-$, $[(C_1-C_6)\text{alkyl}]-C(=O)-O-$ and $[(C_1-C_6)\text{alkyl}]-SO_2-$; $(C_1-C_6)\text{alkyl}$ optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, $[(C_1-C_6)\text{alkyl}]-C(=O)-$, $(C_1-C_6)\text{alkoxy}$, $[(C_1-C_6)\text{alkoxy}]-C(=O)-$, $R^{a1}R^{a2}N-$ and $R^{a3}R^{a4}N-C(=O)-$, wherein R^{a1} , R^{a2} , R^{a3} and R^{a4} are independently selected from hydrogen, $(C_1-C_6)\text{alkyl}$, $[(C_1-C_6)\text{alkyl}]-C(=O)-$, $[(C_1-C_6)\text{alkoxy}]-C(=O)-$ and $[(C_1-C_6)\text{alkyl}]-SO_2-$; and $[C(=O)-NR^{Z11}R^{Z12}]$ wherein R^{Z11} and R^{Z12} are independently selected from hydrogen and $(C_1-C_6)\text{alkyl}$ optionally substituted with one to three substituents independently selected from
10 halo, hydroxy, carboxy, $[(C_1-C_6)\text{alkyl}]-C(=O)-$, $(C_1-C_6)\text{alkoxy}$, $[(C_1-C_6)\text{alkoxy}]-C(=O)-$, $R^{a1}R^{a2}N-$ and $R^{a3}R^{a4}N-C(=O)-$, wherein R^{a1} , R^{a2} , R^{a3} and R^{a4} are independently selected from hydrogen, $(C_1-C_6)\text{alkyl}$, $[(C_1-C_6)\text{alkyl}]-C(=O)-$, $[(C_1-C_6)\text{alkoxy}]-C(=O)-$ and $[(C_1-C_6)\text{alkyl}]-SO_2-$.
15

20 The compounds of the present invention have binding affinity for opioid receptor-like 1 (hereinafter referred to as "ORL-1 receptor").

It is therefore an object of the present invention to provide a compound of formula I which is useful as a ligand for ORL-1 receptor.

It is another object of the present invention to provide a compound of formula
25 I which is a modulator of ORL-1 receptor.

It is another object of the present invention to provide a compound of formula I having selective affinity for ORL-1 receptor. Preferably, these compounds have selective affinity for ORL-1 receptor than μ -receptor.

It is another object of the present invention to provide a compound of formula
30 I having antagonist activity for ORL-1 receptor.

It is another object of the present invention to provide a compound of formula I having selectivity for ORL-1 receptor and antagonist effect for said receptor.

The present invention relates to use of a compound of formula I as a ligand or a modulator for ORL-1 receptor, preferably as a selective ligand for said receptor, more preferably as an antagonist for said receptor, and most preferably as a selective antagonist for said receptor.

5

DETAILED DESCRIPTION OF THE INVENTION

The term "pain" as used herein includes acute and chronic pain; neuropathic or inflammatory pain such as post herpetic neuralgia, neuralgia, diabetic neuropathy or post operative pain; osteoarthritis or back pain; pain in pregnancy labor and pains known to those skilled in the art (e.g., the pains described in *Advances in Pain Research and Therapy*, edited by C. R. Chapman *et al.*, and published by Ravan Press (1989)).

The term "alkyl", as used herein, means a straight or branched saturated monovalent hydrocarbon radical including, but not limited to, methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl, tert-butyl and the like.

The term "cycloalkyl", as used herein, means a saturated carbocyclic radical including, but not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl, cyclodecyl and the like.

The term "alkoxy", as used herein, means an O-alkyl group wherein "alkyl" is defined above.

The term "halo", as used herein, refers to F, Cl, Br or I, preferably F or Cl.

The term "treating", as used herein, refers to reversing, alleviating, inhibiting the progress of, or preventing the disorder or condition to which such term applies, or one or more symptoms of such disorder or condition. The term "treatment" as used herein refers to the act of treating, as "treating" is defined immediately above.

A preferred class of compound of formula (I) of this invention is that wherein:
all R¹ are hydrogen
each R² is independently selected from hydrogen and halo;
X¹ is selected from (CH₂)_{n1} wherein n1 is an integer selected from 1, 2 and 3; O; NH;
S; C(=O); SO₂; and N[(C₁-C₄)alkyl];
X² is selected from CH₂; O; NH; S; C(=O); SO₂; and N[(C₁-C₄)alkyl]; or

30

X^1 and X^2 taken together form $CH=CH$;

W^1 and W^2 are independently selected from $CR^{W1}R^{W2}$, wherein

R^{W1} and R^{W2} are independently selected from hydrogen; halo; hydroxy; (C_1-C_6) alkyl optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, $[(C_1-C_6)alkyl]-C(=O)-$, $(C_1-C_6)alkoxy$, $[(C_1-C_6)alkoxy]-C(=O)-$, $R^{a1}R^{a2}N-$ and $R^{a3}R^{a4}N-C(=O)-$, wherein R^{a1} , R^{a2} , R^{a3} and R^{a4} are independently selected from hydrogen, $(C_1-C_6)alkyl$, $[(C_1-C_6)alkyl]-C(=O)-$, $[(C_1-C_6)alkoxy]-C(=O)-$ and $[(C_1-C_6)alkyl]-SO_2-$; $(C_1-C_6)alkoxy$ optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, $[(C_1-C_6)alkyl]-C(=O)-$, $(C_1-C_6)alkoxy$, $[(C_1-C_6)alkoxy]-C(=O)-$, $R^{a5}R^{a6}N-$ and $R^{a7}R^{a8}N-C(=O)-$, wherein R^{a5} , R^{a6} , R^{a7} and R^{a8} are independently selected from hydrogen, $(C_1-C_6)alkyl$, $[(C_1-C_6)alkyl]-C(=O)-$, $[(C_1-C_6)alkoxy]-C(=O)-$ and $[(C_1-C_6)alkyl]-SO_2-$; $C(=O)-[(C_1-C_6)alkyl]$ wherein said $(C_1-C_6)alkyl$ is optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, $[(C_1-C_6)alkyl]-C(=O)-$, $(C_1-C_6)alkoxy$, $[(C_1-C_6)alkoxy]-C(=O)-$, $R^{a1}R^{a2}N-$ and $R^{a3}R^{a4}N-C(=O)-$, wherein R^{a1} , R^{a2} , R^{a3} and R^{a4} are independently selected from hydrogen, $(C_1-C_6)alkyl$, $[(C_1-C_6)alkyl]-C(=O)-$, $[(C_1-C_6)alkoxy]-C(=O)-$ and $[(C_1-C_6)alkyl]-SO_2-$; $C(=O)-NR^{W11}R^{W12}$ wherein R^{W11} and R^{W12} are independently selected from hydrogen and $(C_1-C_6)alkyl$ optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, $[(C_1-C_6)alkyl]-C(=O)-$, $(C_1-C_6)alkoxy$, $[(C_1-C_6)alkoxy]-C(=O)-$, $R^{a1}R^{a2}N-$ and $R^{a3}R^{a4}N-C(=O)-$, wherein R^{a1} , R^{a2} , R^{a3} and R^{a4} are independently selected from hydrogen, $(C_1-C_6)alkyl$, $[(C_1-C_6)alkyl]-C(=O)-$, $[(C_1-C_6)alkoxy]-C(=O)-$ and $[(C_1-C_6)alkyl]-SO_2-$; $NR^{W13}R^{W14}$ wherein R^{W13} and R^{W14} are independently selected from hydrogen and $(C_1-C_6)alkyl$ optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, $[(C_1-C_6)alkyl]-C(=O)-$, $(C_1-C_6)alkoxy$, $[(C_1-C_6)alkoxy]-C(=O)-$, $R^{a1}R^{a2}N-$ and $R^{a3}R^{a4}N-C(=O)-$, wherein R^{a1} , R^{a2} , R^{a3} and R^{a4} are independently selected from hydrogen, $(C_1-C_6)alkyl$, $[(C_1-C_6)alkyl]-C(=O)-$, $[(C_1-C_6)alkoxy]-C(=O)-$ and $[(C_1-C_6)alkyl]-SO_2-$; aryl selected from phenyl and naphthyl; and four- to eight-membered heterocyclyl containing one to four hetero atoms independently selected from nitrogen, oxygen and sulfur;

A is AB wherein

5 Y^b and Y^c are independently selected from $C(=O)$; $CR^{Y1}R^{Y2}$; $CR^{Y3}[C(=O)R^{Y4}]$; $CR^{Y3}[C(=O)NR^{Y6}R^{Y7}]$; $CR^{Y3}[NR^{Y6}R^{Y7}]$; O; S; SO_2 ; NH; $N[(C_1-C_6)alkyl]$ wherein said $(C_1-C_6)alkyl$ is optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, $[(C_1-C_6)alkyl]-C(=O)-$, $(C_1-C_6)alkoxy$, $[(C_1-C_6)alkoxy]-C(=O)-$, $R^{a1}R^{a2}N-$ and $R^{a3}R^{a4}N-C(=O)-$, wherein R^{a1} , R^{a2} , R^{a3} and R^{a4} are independently selected from hydrogen, $(C_1-C_6)alkyl$, $[(C_1-C_6)alkyl]-C(=O)-$, $[(C_1-C_6)alkoxy]-C(=O)-$ and $[(C_1-C_6)alkyl]-SO_2-$; $N-(CH_2)_{n3}$ -heterocyclyl wherein $n3$ is an integer selected from 0, 1, 2 and 3, and said heterocyclyl contains from four to eight ring atoms one or two of which are independently selected from nitrogen, oxygen and sulfur; $N-(CH_2)_{n4}$ -aryl wherein $n4$ is an integer selected from 0, 1, 2 and 3, and said aryl is selected from phenyl and naphthyl; and $N-(CH_2)_{n5}$ -heteroaryl wherein $n5$ is an integer selected from 0, 1, 2 and 3, and said heteroaryl is a five to ten membered aromatic heterocyclyl containing from one to four hetero atoms independently selected from nitrogen, oxygen and sulfur; or

Y^b and Y^c taken together form a group selected from $CR^{Y81}=CR^{Y82}$; $CR^{Y83}=N$ and $N=N$; and Y^d , Y^e , Y^f , Y^g and Y^h are defined as above;

20 R^{Y1} and R^{Y2} are independently selected from hydrogen; hydroxy; non-, mono- and di-substituted amino wherein the substituents are independently selected from $(C_1-C_6)alkyl$; $[(C_1-C_6)alkyl]-C(=O)-$; $[(C_1-C_6)alkoxy]-C(=O)-$; $[(C_1-C_6)alkyl]-SO_2-$; and four- to eight-membered heterocyclyl containing one to four hetero atoms independently selected from nitrogen, oxygen and sulfur, wherein said heterocyclyl is optionally substituted with one to three substituents independently selected from hydroxy, $(C_1-C_6)alkyl$, $NH_2-C(=O)-$, $[(C_1-C_6)alkyl]-NH-C(=O)-$, $[(C_1-C_6)alkyl]_2-N-C(=O)-$, and non-, mono- and di-substituted amino wherein the substituents are independently selected from $(C_1-C_6)alkyl$, $[(C_1-C_6)alkyl]-C(=O)-$, $[(C_1-C_6)alkoxy]-C(=O)-$ and $[(C_1-C_6)alkyl]-SO_2-$; $(C_1-C_6)alkyl$ optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, $[(C_1-C_6)alkyl]-C(=O)-$, $(C_1-C_6)alkoxy$, $[(C_1-C_6)alkoxy]-C(=O)-$, $R^{a1}R^{a2}N-$ and $R^{a3}R^{a4}N-C(=O)-$, wherein R^{a1} , R^{a2} , R^{a3} and R^{a4} are independently selected from

hydrogen, (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-; and (C₁-C₆)alkoxy optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, [(C₁-C₆)alkyl]-C(=O)-, (C₁-C₆)alkoxy, [(C₁-C₆)alkoxy]-C(=O)-, R^{a5}R^{a6}N- and R^{a7}R^{a8}N-C(=O)-, wherein R^{a5}, R^{a6}, R^{a7} and R^{a8} are independently selected from hydrogen, (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-; or

R^{Y1} and R^{Y2} taken together with the carbon atom to which they are attached form spiropyrrolidinyl or spiropiperidinyl, both of which are optionally N-substituted with a substituent selected from (C₁-C₆)alkyl, (C₁-C₆)alkyl-C(=O)-, [(C₁-C₆)alkyl]-C(=O)-(C₁-C₆)alkyl and aryl-C(=O)- wherein aryl is selected from phenyl and naphthyl;

R^{Y3} is hydrogen;

R^{Y4} is selected from hydroxy; (C₁-C₆)alkyl optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, [(C₁-C₆)alkyl]-C(=O)-, (C₁-C₆)alkoxy, [(C₁-C₆)alkoxy]-C(=O)-, R^{a1}R^{a2}N- and R^{a3}R^{a4}N-C(=O)-, wherein R^{a1}, R^{a2}, R^{a3} and R^{a4} are independently selected from hydrogen, (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-; and (C₁-C₆)alkoxy optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, [(C₁-C₆)alkyl]-C(=O)-, (C₁-C₆)alkoxy, [(C₁-C₆)alkoxy]-C(=O)-, R^{a5}R^{a6}N- and R^{a7}R^{a8}N-C(=O)-, wherein R^{a5}, R^{a6}, R^{a7} and R^{a8} are independently selected from hydrogen, (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-; and

R^{Y5}, R^{Y6} and R^{Y7} are independently selected from hydrogen; (C₁-C₆)alkyl optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, [(C₁-C₆)alkyl]-C(=O)-, (C₁-C₆)alkoxy, [(C₁-C₆)alkoxy]-C(=O)-, R^{a1}R^{a2}N- and R^{a3}R^{a4}N-C(=O)-, wherein R^{a1}, R^{a2}, R^{a3} and R^{a4} are independently selected from hydrogen, (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-; heterocyclyl-(CH₂)_{n6}- wherein n₆ is an integer selected from 0, 1, 2, 3 and 4 and said heterocyclyl is four to eight membered containing one to three hetero atoms independently selected

from nitrogen, oxygen and sulfur, wherein said heterocyclyl is optionally substituted with one to three substituents independently selected from hydroxy; (C₁-C₆)alkyl; NH₂-C(O=)-; (C₁-C₆)alkyl-NH-C(=O)-; [(C₁-C₆)alkyl]₂-N-C(=O)-; and non-, mono- and di-substituted amino wherein the substituents are independently selected from (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-; and hetroaryl-(CH₂)_{n7}- wherein n7 is an integer selected from 0, 1, 2, 3 and 4 and said heteroaryl is five to ten membered containing one to three hetero atoms independently selected from nitrogen, oxygen and sulfur, wherein said heteroaryl is optionally substituted with one to three substituents independently selected from hydroxy; (C₁-C₆)alkyl; NH₂-C(O=)-; (C₁-C₆)alkyl-NH-C(=O)-; [(C₁-C₆)alkyl]₂-N-C(=O)-; and non-, mono- and di-substituted amino wherein the substituents are independently selected from (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-; or

R^{Y6} and R^{Y7} taken together with the nitrogen atom to which they are attached form a four to eight heterocyclyl optionally containing, in addition to the nitrogen atom, one to two additional hetero atoms independently selected from nitrogen, oxygen and sulfur, and said heterocyclyl is optionally substituted with one substituent selected from hydroxy; (C₁-C₆)alkyl; NH₂-C(O=)-; (C₁-C₆)alkyl-NH-C(=O)-; [(C₁-C₆)alkyl]₂-N-C(=O)-; and non-, mono- and di-substituted amino wherein the substituents are independently selected from (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-;

R^{Y81}, R^{Y82} and R^{Y83} are independently selected from R^{Y811} and R^{Y812}C(=O)- wherein R^{Y811} and R^{Y812} are independently selected from hydrogen; hydroxy; (C₁-C₆)alkyl optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, [(C₁-C₆)alkyl]-C(=O)-, (C₁-C₆)alkoxy, [(C₁-C₆)alkoxy]-C(=O)-, R^{a1}R^{a2}N- and R^{a3}R^{a4}N-C(=O)-, wherein R^{a1}, R^{a2}, R^{a3} and R^{a4} are independently selected from hydrogen, (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-; and (C₁-C₆)alkoxy optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, [(C₁-C₆)alkyl]-C(=O)-, (C₁-C₆)alkoxy, [(C₁-

C_6)alkoxy]-C(=O)-, $R^{a5}R^{a6}N$ - and $R^{a7}R^{a8}N$ -C(=O)-, wherein R^{a5} , R^{a6} , R^{a7} and R^{a8} are independently selected from hydrogen, (C_1-C_6) alkyl, $[(C_1-C_6)alkyl]-C(=O)-$, $[(C_1-C_6)alkoxy]-C(=O)-$ and $[(C_1-C_6)alkyl]-SO_2-$; and

said A is optionally substituted in the fused benzene rings with one to four substituents
 5 independently selected from halo; hydroxy; mercapto; phenyl; (C_1-C_6) alkyl optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, $[(C_1-C_6)alkyl]-C(=O)-$, $(C_1-C_6)alkoxy$, $[(C_1-C_6)alkoxy]-C(=O)-$, $R^{a1}R^{a2}N$ - and $R^{a3}R^{a4}N$ -C(=O)-, wherein R^{a1} , R^{a2} , R^{a3} and R^{a4} are independently selected from hydrogen, $(C_1-C_6)alkyl$, $[(C_1-C_6)alkyl]-C(=O)-$, $[(C_1-C_6)alkoxy]-C(=O)-$ and $[(C_1-C_6)alkyl]-SO_2-$;
 10 C_6)alkyl]- SO_2- ; and $(C_1-C_6)alkoxy$ optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, $[(C_1-C_6)alkyl]-C(=O)-$, $(C_1-C_6)alkoxy$, $[(C_1-C_6)alkoxy]-C(=O)-$, $R^{a5}R^{a6}N$ - and $R^{a7}R^{a8}N$ -C(=O)-, wherein R^{a5} , R^{a6} , R^{a7} and R^{a8} are independently selected from hydrogen, $(C_1-C_6)alkyl$, $[(C_1-C_6)alkyl]-C(=O)-$, $[(C_1-C_6)alkoxy]-C(=O)-$ and $[(C_1-C_6)alkyl]-SO_2-$; and
 15 Z is selected from C(=O); $(CH_2)_{n8}$ wherein n8 is an integer selected from 0, 1 and 2; and CHR^{Z1} wherein

R^{Z1} is selected from carboxy; $(C_1-C_6)alkoxy-C(=O)-$; non-, mono- and di-substituted amino wherein the substituents are independently selected from $(C_1-C_6)alkyl$, $[(C_1-C_6)alkyl]-C(=O)-$, $[(C_1-C_6)alkyl]-C(=O)-O-$ and $[(C_1-C_6)alkyl]-SO_2-$;
 20 $(C_1-C_6)alkyl$ optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, $[(C_1-C_6)alkyl]-C(=O)-$, $(C_1-C_6)alkoxy$, $[(C_1-C_6)alkoxy]-C(=O)-$, $R^{a1}R^{a2}N$ - and $R^{a3}R^{a4}N$ -C(=O)-, wherein R^{a1} , R^{a2} , R^{a3} and R^{a4} are independently selected from hydrogen, $(C_1-C_6)alkyl$, $[(C_1-C_6)alkyl]-C(=O)-$, $[(C_1-C_6)alkoxy]-C(=O)-$ and $[(C_1-C_6)alkyl]-SO_2-$; and
 25 $[C(=O)-NR^{Z11}R^{Z12}]$ wherein R^{Z11} and R^{Z12} are independently selected from hydrogen and $(C_1-C_6)alkyl$ optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, $[(C_1-C_6)alkyl]-C(=O)-$, $(C_1-C_6)alkoxy$, $[(C_1-C_6)alkoxy]-C(=O)-$, $R^{a1}R^{a2}N$ - and $R^{a3}R^{a4}N$ -C(=O)-, wherein R^{a1} , R^{a2} , R^{a3} and R^{a4} are independently selected from hydrogen, $(C_1-C_6)alkyl$, $[(C_1-C_6)alkyl]-C(=O)-$, $[(C_1-C_6)alkoxy]-C(=O)-$ and $[(C_1-C_6)alkyl]-SO_2-$.
 30

A further preferred class of compound of formula (I) of this invention is that

wherein:

all R^1 are hydrogen

each R^2 is independently selected from hydrogen and halo;

X^1 is selected from $(CH_2)_{n1}$ wherein $n1$ is an integer selected from 1, 2 and 3; O; NH;

5 S; C(=O); SO_2 ; and N[(C₁-C₄)alkyl];

X^2 is selected from CH_2 ; O; NH; S; C(=O); SO_2 ; and N[(C₁-C₄)alkyl]; or

X^1 and X^2 taken together form CH=CH;

W^1 and W^2 are both CH_2 ;

A is AB wherein

10 both Y^b and Y^c are independently selected from C(=O); $CR^{Y1}R^{Y2}$; $CR^{Y3}[C(=O)R^{Y4}]$; $CR^{Y3}[C(=O)NR^{Y6}R^{Y7}]$; and $CR^{Y3}[NR^{Y6}R^{Y7}]$, wherein

R^{Y1} and R^{Y2} are independently selected from hydrogen; hydroxy; non-, mono- and di-substituted amino wherein the substituents are independently selected from (C₁-C₆)alkyl; [(C₁-C₆)alkyl]-C(=O)-; [(C₁-C₆)alkoxy]-C(=O)-; [(C₁-C₆)alkyl]- SO_2 -; and four- to eight-membered heterocyclyl containing one to four hetero atoms independently selected from nitrogen, oxygen and sulfur, wherein said heterocyclyl is optionally substituted with one to three substituents independently selected from hydroxy, (C₁-C₆)alkyl, $NH_2-C(=O)-$, [(C₁-C₆)alkyl]-NH-C(=O)-, [(C₁-C₆)alkyl]₂-N-C(=O)-, and non-, mono- and di-substituted amino wherein the substituents are independently selected from (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]- SO_2 -; (C₁-C₆)alkyl optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, [(C₁-C₆)alkyl]-C(=O)-, (C₁-C₆)alkoxy, [(C₁-C₆)alkoxy]-C(=O)-, $R^{a1}R^{a2}N-$ and $R^{a3}R^{a4}N-C(=O)-$, wherein R^{a1} , R^{a2} , R^{a3} and R^{a4} are independently selected from hydrogen, (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]- SO_2 -; and (C₁-C₆)alkoxy optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, [(C₁-C₆)alkyl]-C(=O)-, (C₁-C₆)alkoxy, [(C₁-C₆)alkoxy]-C(=O)-, $R^{a5}R^{a6}N-$ and $R^{a7}R^{a8}N-C(=O)-$, wherein R^{a5} , R^{a6} , R^{a7} and R^{a8} are independently selected from hydrogen, (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]- SO_2 -; or

R^{Y1} and R^{Y2} taken together with the carbon atom to which they are attached form spiropyrrolidinyl or spiropiperidinyl, both of which are optionally N-substituted with a substituent selected from (C_1-C_6) alkyl, (C_1-C_6) alkyl-C(=O)-, $[(C_1-C_6)$ alkyl]-C(=O)- (C_1-C_6) alkyl and aryl-(C=O)- wherein aryl is selected from phenyl and naphthyl;

R^{Y3} is hydrogen;

R^{Y4} is selected from hydroxy; (C_1-C_6) alkyl optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, $[(C_1-C_6)$ alkyl]-C(=O)-, (C_1-C_6) alkoxy, $[(C_1-C_6)$ alkoxy]-C(=O)-, $R^{a1}R^{a2}N$ - and $R^{a3}R^{a4}N$ -C(=O)-, wherein R^{a1} , R^{a2} , R^{a3} and R^{a4} are independently selected from hydrogen, (C_1-C_6) alkyl, $[(C_1-C_6)$ alkyl]-C(=O)-, $[(C_1-C_6)$ alkoxy]-C(=O)- and $[(C_1-C_6)$ alkyl]-SO₂-; and (C_1-C_6) alkoxy optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, $[(C_1-C_6)$ alkyl]-C(=O)-, (C_1-C_6) alkoxy, $[(C_1-C_6)$ alkoxy]-C(=O)-, $R^{a5}R^{a6}N$ - and $R^{a7}R^{a8}N$ -C(=O)-, wherein R^{a5} , R^{a6} , R^{a7} and R^{a8} are independently selected from hydrogen, (C_1-C_6) alkyl, $[(C_1-C_6)$ alkyl]-C(=O)-, $[(C_1-C_6)$ alkoxy]-C(=O)- and $[(C_1-C_6)$ alkyl]-SO₂-; and

R^{Y6} and R^{Y7} are independently selected from hydrogen; (C_1-C_6) alkyl optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, $[(C_1-C_6)$ alkyl]-C(=O)-, (C_1-C_6) alkoxy, $[(C_1-C_6)$ alkoxy]-C(=O)-, $R^{a1}R^{a2}N$ - and $R^{a3}R^{a4}N$ -C(=O)-, wherein R^{a1} , R^{a2} , R^{a3} and R^{a4} are independently selected from hydrogen, (C_1-C_6) alkyl, $[(C_1-C_6)$ alkyl]-C(=O)-, $[(C_1-C_6)$ alkoxy]-C(=O)- and $[(C_1-C_6)$ alkyl]-SO₂-; heterocyclyl-(CH₂)_{n6}- wherein n6 is an integer selected from 0, 1, 2, 3 and 4 and said heterocyclyl is four to eight membered containing one to three hetero atoms independently selected from nitrogen, oxygen and sulfur, wherein said heterocyclyl is optionally substituted with one to three substituents independently selected from hydroxy; (C_1-C_6) alkyl; NH₂-C(=O)-; (C_1-C_6) alkyl-NH-C(=O)-; $[(C_1-C_6)$ alkyl]₂-N-C(=O)-; and non-, mono- and di-substituted amino wherein the substituents are independently selected from (C_1-C_6) alkyl, $[(C_1-C_6)$ alkyl]-C(=O)-, $[(C_1-C_6)$ alkoxy]-C(=O)- and $[(C_1-C_6)$ alkyl]-SO₂-; and heteroaryl-(CH₂)_{n7}- wherein n7 is an integer selected from 0, 1, 2, 3 and 4 and said heteroaryl is five to ten

membered containing one to three hetero atoms independently selected from nitrogen, oxygen and sulfur, wherein said heteroaryl is optionally substituted with one to three substituents independently selected from hydroxy; (C₁-C₆)alkyl; NH₂-C(O=)-; (C₁-C₆)alkyl-NH-C(=O)-; [(C₁-C₆)alkyl]₂-N-C(=O)-; and non-, mono- and di-substituted amino wherein the substituents are independently selected from (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-; or

R^{Y6} and R^{Y7} taken together with the nitrogen atom to which they are attached form a four to eight heterocyclyl optionally containing, in addition to the nitrogen atom, one to two additional hetero atoms independently selected from nitrogen, oxygen and sulfur, and said heterocyclyl is optionally substituted with one substituent selected from hydroxy; (C₁-C₆)alkyl; NH₂-C(O=)-; (C₁-C₆)alkyl-NH-C(=O)-; [(C₁-C₆)alkyl]₂-N-C(=O)-; and non-, mono- and di-substituted amino wherein the substituents are independently selected from (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-;

said A is optionally substituted in the fused benzene rings with one to four substituents independently selected from halo; hydroxy; mercapto; phenyl; (C₁-C₆)alkyl optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, [(C₁-C₆)alkyl]-C(=O)-, (C₁-C₆)alkoxy, [(C₁-C₆)alkoxy]-C(=O)-, R^{a1}R^{a2}N- and R^{a3}R^{a4}N-C(=O)-, wherein R^{a1}, R^{a2}, R^{a3} and R^{a4} are independently selected from hydrogen, (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-; and (C₁-C₆)alkoxy optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, [(C₁-C₆)alkyl]-C(=O)-, (C₁-C₆)alkoxy, [(C₁-C₆)alkoxy]-C(=O)-, R^{a5}R^{a6}N- and R^{a7}R^{a8}N-C(=O)-, wherein R^{a5}, R^{a6}, R^{a7} and R^{a8} are independently selected from hydrogen, (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-; and

Z is selected from C(=O); (CH₂)_{n8} wherein n8 is an integer selected from 0, 1 and 2; and CHR^{Z1} wherein

R^{Z1} is selected from carboxy; (C₁-C₆)alkoxy-C(=O)-; non-, mono- and di-substituted amino wherein the substituents are independently selected from (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkyl]-C(=O)-O- and [(C₁-C₆)alkyl]-

SO₂-; (C₁-C₆)alkyl optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, [(C₁-C₆)alkyl]-C(=O)-, (C₁-C₆)alkoxy, [(C₁-C₆)alkoxy]-C(=O)-, R^{a1}R^{a2}N- and R^{a3}R^{a4}N-C(=O)-, wherein R^{a1}, R^{a2}, R^{a3} and R^{a4} are independently selected from hydrogen, (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-; and [C(=O)-NR^{Z11}R^{Z12}] wherein R^{Z11} and R^{Z12} are independently selected from hydrogen and (C₁-C₆)alkyl optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, [(C₁-C₆)alkyl]-C(=O)-, (C₁-C₆)alkoxy, [(C₁-C₆)alkoxy]-C(=O)-, R^{a1}R^{a2}N- and R^{a3}R^{a4}N-C(=O)-, wherein R^{a1}, R^{a2}, R^{a3} and R^{a4} are independently selected from hydrogen, (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-.

A further preferred class of compound of formula (I) of this invention is that wherein

all R¹ are hydrogen

each R² is independently selected from hydrogen and halo;

X¹ is selected from (CH₂)_{n1} wherein n1 is an integer selected from 1, 2 and 3; O; NH; S; C(=O); SO₂; and N[(C₁-C₄)alkyl];

X² is selected from CH₂; O; NH; S; C(=O); SO₂; and N[(C₁-C₄)alkyl]; or

X¹ and X² taken together form CH=CH;

W¹ and W² are both CH₂;

A is AB wherein

Y^b is CR^{Y3}[C(=O)NR^{Y6}R^{Y7}]; and

Y^c is selected from CR^{Y1}R^{Y2}; CR^{Y3}[C(=O)R^{Y4}]; CR^{Y3}[C(=O)NR^{Y6}R^{Y7}]; and

CR^{Y3}[NR^{Y6}R^{Y7}], wherein

R^{Y1} and R^{Y2} are independently selected from hydrogen; hydroxy; non-, mono- and di-substituted amino wherein the substituents are independently selected from (C₁-C₆)alkyl; [(C₁-C₆)alkyl]-C(=O)-; [(C₁-C₆)alkoxy]-C(=O)-; [(C₁-C₆)alkyl]-SO₂-; and four- to eight-membered heterocyclyl containing one to four hetero atoms independently selected from nitrogen, oxygen and sulfur, wherein said heterocyclyl is optionally substituted with one to three substituents independently selected from hydroxy, (C₁-C₆)alkyl, NH₂-C(O=)-,

- $[(C_1-C_6)alkyl]-NH-C(=O)-$, $[(C_1-C_6)alkyl]_2-N-C(=O)-$, and non-, mono- and di-substituted amino wherein the substituents are independently selected from $(C_1-C_6)alkyl$, $[(C_1-C_6)alkyl]-C(=O)-$, $[(C_1-C_6)alkoxy]-C(=O)-$ and $[(C_1-C_6)alkyl]-SO_2-$; $(C_1-C_6)alkyl$ optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, $[(C_1-C_6)alkyl]-C(=O)-$, $(C_1-C_6)alkoxy$, $[(C_1-C_6)alkoxy]-C(=O)-$, $R^{a1}R^{a2}N-$ and $R^{a3}R^{a4}N-C(=O)-$, wherein R^{a1} , R^{a2} , R^{a3} and R^{a4} are independently selected from hydrogen, $(C_1-C_6)alkyl$, $[(C_1-C_6)alkyl]-C(=O)-$, $[(C_1-C_6)alkoxy]-C(=O)-$ and $[(C_1-C_6)alkyl]-SO_2-$; and $(C_1-C_6)alkoxy$ optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, $[(C_1-C_6)alkyl]-C(=O)-$, $(C_1-C_6)alkoxy$, $[(C_1-C_6)alkoxy]-C(=O)-$, $R^{a5}R^{a6}N-$ and $R^{a7}R^{a8}N-C(=O)-$, wherein R^{a5} , R^{a6} , R^{a7} and R^{a8} are independently selected from hydrogen, $(C_1-C_6)alkyl$, $[(C_1-C_6)alkyl]-C(=O)-$, $[(C_1-C_6)alkoxy]-C(=O)-$ and $[(C_1-C_6)alkyl]-SO_2-$; or
- R^{Y1} and R^{Y2} taken together with the carbon atom to which they are attached form spiropyrrolidinyl or spiropiperidinyl, both of which are optionally N-substituted with a substituent selected from $(C_1-C_6)alkyl$, $(C_1-C_6)alkyl-C(=O)-$, $[(C_1-C_6)alkyl]-C(=O)-(C_1-C_6)alkyl$ and aryl- $C(=O)-$ wherein aryl is selected from phenyl and naphthyl;
- R^{Y3} is hydrogen;
- R^{Y4} is selected from hydroxy; $(C_1-C_6)alkyl$ optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, $[(C_1-C_6)alkyl]-C(=O)-$, $(C_1-C_6)alkoxy$, $[(C_1-C_6)alkoxy]-C(=O)-$, $R^{a1}R^{a2}N-$ and $R^{a3}R^{a4}N-C(=O)-$, wherein R^{a1} , R^{a2} , R^{a3} and R^{a4} are independently selected from hydrogen, $(C_1-C_6)alkyl$, $[(C_1-C_6)alkyl]-C(=O)-$, $[(C_1-C_6)alkoxy]-C(=O)-$ and $[(C_1-C_6)alkyl]-SO_2-$; and $(C_1-C_6)alkoxy$ optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, $[(C_1-C_6)alkyl]-C(=O)-$, $(C_1-C_6)alkoxy$, $[(C_1-C_6)alkoxy]-C(=O)-$, $R^{a5}R^{a6}N-$ and $R^{a7}R^{a8}N-C(=O)-$, wherein R^{a5} , R^{a6} , R^{a7} and R^{a8} are independently selected from hydrogen, $(C_1-C_6)alkyl$, $[(C_1-C_6)alkyl]-C(=O)-$, $[(C_1-C_6)alkoxy]-C(=O)-$ and $[(C_1-C_6)alkyl]-SO_2-$; and
- R^{Y5} , R^{Y6} and R^{Y7} are independently selected from hydrogen; $(C_1-C_6)alkyl$

optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, [(C₁-C₆)alkyl]-C(=O)-, (C₁-C₆)alkoxy, [(C₁-C₆)alkoxy]-C(=O)-, R^{a1}R^{a2}N- and R^{a3}R^{a4}N-C(=O)-, wherein R^{a1}, R^{a2}, R^{a3} and R^{a4} are independently selected from hydrogen, (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-; hetrocyclyl-(CH₂)_{n6}- wherein n6 is an integer selected from 0, 1, 2, 3 and 4 and said heterocyclyl is four to eight membered containing one to three hetero atoms independently selected from nitrogen, oxygen and sulfur, wherein said heterocyclyl is optionally substituted with one to three substituents independently selected from hydroxy; (C₁-C₆)alkyl; NH₂-C(O=)-; (C₁-C₆)alkyl-NH-C(=O)-; [(C₁-C₆)alkyl]₂-N-C(=O)-; and non-, mono- and di-substituted amino wherein the substituents are independently selected from (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-; and hetroaryl-(CH₂)_{n7}- wherein n7 is an integer selected from 0, 1, 2, 3 and 4 and said heteroaryl is five to ten membered containing one to three hetero atoms independently selected from nitrogen, oxygen and sulfur, wherein said heteroaryl is optionally substituted with one to three substituents independently selected from hydroxy; (C₁-C₆)alkyl; NH₂-C(O=)-; (C₁-C₆)alkyl-NH-C(=O)-; [(C₁-C₆)alkyl]₂-N-C(=O)-; and non-, mono- and di-substituted amino wherein the substituents are independently selected from (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-; or

R^{Y6} and R^{Y7} taken together with the nitrogen atom to which they are attached form a four to eight heterocyclyl optionally containing, in addition to the nitrogen atom, one to two additional hetero atoms independently selected from nitrogen, oxygen and sulfur, and said heterocyclyl is optionally substituted with one substituent selected from hydroxy; (C₁-C₆)alkyl; NH₂-C(O=)-; (C₁-C₆)alkyl-NH-C(=O)-; [(C₁-C₆)alkyl]₂-N-C(=O)-; and non-, mono- and di-substituted amino wherein the substituents are independently selected from (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-;

said A is optionally substituted in the fused benzene rings with one to four substituents independently selected from halo; hydroxy; mercapto; phenyl; (C₁-C₆)alkyl optionally

substituted with one to three substituents independently selected from halo, hydroxy, carboxy, (C₁-C₆)alkoxy, (C₁-C₆)alkoxy-C(=O)- and non-, mono- and di-substituted amino wherein the substituents are independently selected from (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-; and (C₁-C₆)alkoxy

5 optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, (C₁-C₆)alkoxy, (C₁-C₆)alkoxy-C(=O)- and non-, mono- and di-substituted amino wherein the substituents are independently selected from (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-; and Z is selected from C(=O); (CH₂)_{n8} wherein n8 is an integer selected from 0, 1 and 2;

10 and CHR^{Z1} wherein

R^{Z1} is selected from carboxy; (C₁-C₆)alkoxy-C(=O)-; non-, mono- and di-substituted amino wherein the substituents are independently selected from (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkyl]-C(=O)-O- and [(C₁-C₆)alkyl]-SO₂-; (C₁-C₆)alkyl optionally substituted with one to three substituents

15 independently selected from halo, hydroxy, carboxy, [(C₁-C₆)alkyl]-C(=O)-, (C₁-C₆)alkoxy, [(C₁-C₆)alkoxy]-C(=O)-, R^{a1}R^{a2}N- and R^{a3}R^{a4}N-C(=O)-, wherein R^{a1}, R^{a2}, R^{a3} and R^{a4} are independently selected from hydrogen, (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-; and [C(=O)-NR^{Z11}R^{Z12}] wherein R^{Z11} and R^{Z12} are independently selected from hydrogen and

20 (C₁-C₆)alkyl optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, [(C₁-C₆)alkyl]-C(=O)-, (C₁-C₆)alkoxy, [(C₁-C₆)alkoxy]-C(=O)-, R^{a1}R^{a2}N- and R^{a3}R^{a4}N-C(=O)-, wherein R^{a1}, R^{a2}, R^{a3} and R^{a4} are independently selected from hydrogen, (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-.

25

A further preferred class of compound of formula (I) of this invention is that wherein,

all R¹ are hydrogen

each R² is independently selected from hydrogen and halo;

30 X¹ is selected from (CH₂)_{n1} wherein n1 is an integer selected from 1, 2 and 3; O; NH; S; C(=O); SO₂; and N[(C₁-C₄)alkyl];

X² is selected from CH₂; O; NH; S; C(=O); SO₂; and N[(C₁-C₄)alkyl]; or

X^1 and X^2 taken together form $CH=CH$;

W^1 and W^2 are both CH_2 ;

A is AB wherein

Y^b is $CR^{Y3}[C(=O)NR^{Y6}R^{Y7}]$; and

5 Y^c is selected from $CR^{Y1}R^{Y2}$; $CR^{Y3}[C(=O)R^{Y4}]$; $CR^{Y3}[C(=O)NR^{Y6}R^{Y7}]$; and $CR^{Y3}[NR^{Y6}R^{Y7}]$; wherein

R^{Y1} and R^{Y2} are independently selected from hydrogen; hydroxy; non-, mono- and di-substituted amino wherein the substituents are independently selected from (C_1-C_6) alkyl; $[(C_1-C_6)alkyl]-C(=O)-$; $[(C_1-C_6)alkoxy]-C(=O)-$; $[(C_1-C_6)alkyl]-SO_2-$; and four- to eight-membered heterocyclyl containing one to four hetero atoms independently selected from nitrogen, oxygen and sulfur, wherein said heterocyclyl is optionally substituted with one to three substituents independently selected from hydroxy, $(C_1-C_6)alkyl$, $NH_2-C(=O)-$, $[(C_1-C_6)alkyl]-NH-C(=O)-$, $[(C_1-C_6)alkyl]_2-N-C(=O)-$, and non-, mono- and di-substituted amino wherein the substituents are independently selected from $(C_1-C_6)alkyl$, $[(C_1-C_6)alkyl]-C(=O)-$, $[(C_1-C_6)alkoxy]-C(=O)-$ and $[(C_1-C_6)alkyl]-SO_2-$; $(C_1-C_6)alkyl$ optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, $[(C_1-C_6)alkyl]-C(=O)-$, $(C_1-C_6)alkoxy$, $[(C_1-C_6)alkoxy]-C(=O)-$, $R^{a1}R^{a2}N-$ and $R^{a3}R^{a4}N-C(=O)-$, wherein R^{a1} , R^{a2} , R^{a3} and R^{a4} are independently selected from hydrogen, $(C_1-C_6)alkyl$, $[(C_1-C_6)alkyl]-C(=O)-$, $[(C_1-C_6)alkoxy]-C(=O)-$ and $[(C_1-C_6)alkyl]-SO_2-$; and $(C_1-C_6)alkoxy$ optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, $[(C_1-C_6)alkyl]-C(=O)-$, $(C_1-C_6)alkoxy$, $[(C_1-C_6)alkoxy]-C(=O)-$, $R^{a5}R^{a6}N-$ and $R^{a7}R^{a8}N-C(=O)-$, wherein R^{a5} , R^{a6} , R^{a7} and R^{a8} are independently selected from hydrogen, $(C_1-C_6)alkyl$, $[(C_1-C_6)alkyl]-C(=O)-$, $[(C_1-C_6)alkoxy]-C(=O)-$ and $[(C_1-C_6)alkyl]-SO_2-$; or

R^{Y1} and R^{Y2} taken together with the carbon atom to which they are attached form spiropyrrolidiny1 or spiropiperidiny1, both of which are optionally N-substituted with a substituent selected from $(C_1-C_6)alkyl$, $(C_1-C_6)alkyl-C(=O)-$, $[(C_1-C_6)alkyl]-C(=O)-(C_1-C_6)alkyl$ and aryl- $C(=O)-$ wherein aryl is selected from phenyl and naphthyl;

R^{Y3} is hydrogen;

R^{Y4} is selected from hydroxy; (C_1-C_6) alkyl optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, $[(C_1-C_6)alkyl]-C(=O)-$, $(C_1-C_6)alkoxy$, $[(C_1-C_6)alkoxy]-C(=O)-$, $R^{a1}R^{a2}N-$ and $R^{a3}R^{a4}N-C(=O)-$, wherein R^{a1} , R^{a2} , R^{a3} and R^{a4} are independently selected from hydrogen, $(C_1-C_6)alkyl$, $[(C_1-C_6)alkyl]-C(=O)-$, $[(C_1-C_6)alkoxy]-C(=O)-$ and $[(C_1-C_6)alkyl]-SO_2-$; and $(C_1-C_6)alkoxy$ optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, $[(C_1-C_6)alkyl]-C(=O)-$, $(C_1-C_6)alkoxy$, $[(C_1-C_6)alkoxy]-C(=O)-$, $R^{a5}R^{a6}N-$ and $R^{a7}R^{a8}N-C(=O)-$, wherein R^{a5} , R^{a6} , R^{a7} and R^{a8} are independently selected from hydrogen, $(C_1-C_6)alkyl$, $[(C_1-C_6)alkyl]-C(=O)-$, $[(C_1-C_6)alkoxy]-C(=O)-$ and $[(C_1-C_6)alkyl]-SO_2-$; and

R^{Y5} , R^{Y6} and R^{Y7} are independently selected from hydrogen; $(C_1-C_6)alkyl$ optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, $[(C_1-C_6)alkyl]-C(=O)-$, $(C_1-C_6)alkoxy$, $[(C_1-C_6)alkoxy]-C(=O)-$, $R^{a1}R^{a2}N-$ and $R^{a3}R^{a4}N-C(=O)-$, wherein R^{a1} , R^{a2} , R^{a3} and R^{a4} are independently selected from hydrogen, $(C_1-C_6)alkyl$, $[(C_1-C_6)alkyl]-C(=O)-$, $[(C_1-C_6)alkoxy]-C(=O)-$ and $[(C_1-C_6)alkyl]-SO_2-$; heterocyclyl- $(CH_2)_{n6}-$ wherein $n6$ is an integer selected from 0, 1, 2, 3 and 4 and said heterocyclyl is four to eight membered containing one to three hetero atoms independently selected from nitrogen, oxygen and sulfur, wherein said heterocyclyl is optionally substituted with one to three substituents independently selected from hydroxy; $(C_1-C_6)alkyl$; $NH_2-C(=O)-$; $(C_1-C_6)alkyl-NH-C(=O)-$; $[(C_1-C_6)alkyl]_2-N-C(=O)-$; and non-, mono- and di-substituted amino wherein the substituents are independently selected from $(C_1-C_6)alkyl$, $[(C_1-C_6)alkyl]-C(=O)-$, $[(C_1-C_6)alkoxy]-C(=O)-$ and $[(C_1-C_6)alkyl]-SO_2-$; and heteroaryl- $(CH_2)_{n7}-$ wherein $n7$ is an integer selected from 0, 1, 2, 3 and 4 and said heteroaryl is five to ten membered containing one to three hetero atoms independently selected from nitrogen, oxygen and sulfur, wherein said heteroaryl is optionally substituted with one to three substituents independently selected from hydroxy; $(C_1-C_6)alkyl$; $NH_2-C(=O)-$; $(C_1-C_6)alkyl-NH-C(=O)-$; $[(C_1-C_6)alkyl]_2-N-C(=O)-$; and non-, mono- and di-substituted amino wherein the substituents are

independently selected from (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-; or

R^{Y6} and R^{Y7} taken together with the nitrogen atom to which they are attached form a four to eight heterocyclyl optionally containing, in addition to the nitrogen atom, one to two additional hetero atoms independently selected from nitrogen, oxygen and sulfur, and said heterocyclyl is optionally substituted with one substituent selected from hydroxy; (C₁-C₆)alkyl; NH₂-C(O=)-; (C₁-C₆)alkyl-NH-C(=O)-; [(C₁-C₆)alkyl]₂-N-C(=O)-; and non-, mono- and di-substituted amino wherein the substituents are independently selected from (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-;

said A is optionally substituted in the fused benzene rings with one to four substituents independently selected from halo; hydroxy; mercapto; phenyl; (C₁-C₆)alkyl optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, (C₁-C₆)alkoxy, (C₁-C₆)alkoxy-C(=O)- and non-, mono- and di-substituted amino wherein the substituents are independently selected from (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-; and (C₁-C₆)alkoxy optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, (C₁-C₆)alkoxy, (C₁-C₆)alkoxy-C(=O)- and non-, mono- and di-substituted amino wherein the substituents are independently selected from (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-; and Z is C(=O).

Individual preferred compounds of this invention include

2,3-dihydro-1'-{3-[2-(N-methylaminocarbonyl)indolin-1-yl]-3-oxopropyl}spiro[1H-indene-1,4'-piperidine];
 2,3-dihydro-1'-[3-(2-N,N-dimethylaminocarbonylindolin-1-yl)-3-oxopropyl]spiro[1H-indene-1,4'-piperidine];
 2,3-dihydro-1'-[3-(2-morpholinocarbonylindolin-1-yl)-3-oxopropyl]spiro[1H-indene-1,4'-piperidine];
 2,3-dihydro-1'-[3-(2-carbamoylindolin-1-yl)-3-oxopropyl]spiro[1H-indene-1,4'-piperidine] hydrochloride;

- 2,3-dihydro-1'-{3-[2-(1-ethylprrolydin-3-yl)aminocarbonylindolin-1-yl]-3-oxopropyl}spiro[1*H*-indene-1,4'-piperidine];
- 2,3-dihydro-1'-{3-[2-(*S*)-(N,N-dimethylaminoethyl)aminocarbonylindolin-1-yl]-3-oxopropyl}spiro[1*H*-indene-1,4'-piperidine];
- 5 2,3-dihydro-1'-{3-[2-(*S*)-(2-hydroxyethyl)aminocarbonylindolin-1-yl]-3-oxopropyl}spiro[1*H*-indene-1,4'-piperidine];
- 2,3-dihydro-1'-{3-[2-(*S*)-(2-aminoethyl)aminocarbonylindolin-1-yl]-3-oxopropyl}spiro[1*H*-indene-1,4'-piperidine];
- 2,3-dihydro-1'-{3-[2-(*S*)-(2-acetamidoethyl)aminocarbonylindolin-1-yl]-3-oxopropyl}spiro[1*H*-indene-1,4'-piperidine];
- 10 2,3-dihydro-1'-{3-[2-(*S*)-(2-methanesulfonamidoethyl)aminocarbonylindolin-1-yl]-3-oxopropyl}spiro[1*H*-indene-1,4'-piperidine];
- 2,3-dihydro-1'-[3-(2-(*S*)-*N*-methylaminocarbonylindolin-1-yl)-3-oxopropyl]spiro[1*H*-indene-1,4'-piperidine];
- 15 2,3-dihydro-1'-[3-(2-(*S*)-*N,N*-dimethylaminocarbonylindolin-1-yl)-3-oxopropyl]spiro[1*H*-indene-1,4'-piperidine];
- 2,3-dihydro-1'-{3-[2-(*S*)-(4-morpholinecarbonyl)indolin-1-yl]-3-oxopropyl}spiro[1*H*-indene-1,4'-piperidine]; and
- 2,3-dihydro-1'-[3-(2-(*S*)-aminocarbonylindolin-1-yl)-3-oxopropyl]spiro[1*H*-indene-
- 20 1,4'-piperidine], or a salt thereof.

Another preferred class of compounds of formula (I) of this invention is that wherein

- all R¹ are hydrogen
- 25 each R² is independently selected from hydrogen and halo;
- X¹ is selected from (CH₂)_{n1} wherein n1 is an integer selected from 1, 2 and 3; O; NH; S; C(=O); SO₂; and N[(C₁-C₄)alkyl];
- X² is selected from CH₂; O; NH; S; C(=O); SO₂; and N[(C₁-C₄)alkyl]; or
- X¹ and X² taken together form CH=CH;
- 30 W¹ and W² are both CH₂;
- A is AB wherein
- Y^b is CR^{Y1}R^{Y2}; and

Y^c is selected from $CR^{Y1}R^{Y2}$; $CR^{Y3}[C(=O)R^{Y4}]$; $CR^{Y3}[C(=O)NR^{Y6}R^{Y7}]$; and $CR^{Y3}[NR^{Y6}R^{Y7}]$; or

Y^b and Y^c taken together form a group selected from CH_2-CH_2 and $CH_2=CH_2$;

R^{Y1} and R^{Y2} are independently selected from hydrogen; hydroxy; non-, mono- and di-substituted amino wherein the substituents are independently selected from (C_1-C_6) alkyl; $[(C_1-C_6)alkyl]-C(=O)-$; $[(C_1-C_6)alkoxy]-C(=O)-$; $[(C_1-C_6)alkyl]-SO_2-$; and four- to eight-membered heterocyclyl containing one to four hetero atoms independently selected from nitrogen, oxygen and sulfur, wherein said heterocyclyl is optionally substituted with one to three substituents independently selected from hydroxy, $(C_1-C_6)alkyl$, $NH_2-C(=O)-$, $[(C_1-C_6)alkyl]-NH-C(=O)-$, $[(C_1-C_6)alkyl]_2-N-C(=O)-$, and non-, mono- and di-substituted amino wherein the substituents are independently selected from $(C_1-C_6)alkyl$, $[(C_1-C_6)alkyl]-C(=O)-$, $[(C_1-C_6)alkoxy]-C(=O)-$ and $[(C_1-C_6)alkyl]-SO_2-$; $(C_1-C_6)alkyl$ optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, $[(C_1-C_6)alkyl]-C(=O)-$, $(C_1-C_6)alkoxy$, $[(C_1-C_6)alkoxy]-C(=O)-$, $R^{a1}R^{a2}N-$ and $R^{a3}R^{a4}N-C(=O)-$, wherein R^{a1} , R^{a2} , R^{a3} and R^{a4} are independently selected from hydrogen, $(C_1-C_6)alkyl$, $[(C_1-C_6)alkyl]-C(=O)-$, $[(C_1-C_6)alkoxy]-C(=O)-$ and $[(C_1-C_6)alkyl]-SO_2-$; and $(C_1-C_6)alkoxy$ optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, $[(C_1-C_6)alkyl]-C(=O)-$, $(C_1-C_6)alkoxy$, $[(C_1-C_6)alkoxy]-C(=O)-$, $R^{a5}R^{a6}N-$ and $R^{a7}R^{a8}N-C(=O)-$, wherein R^{a5} , R^{a6} , R^{a7} and R^{a8} are independently selected from hydrogen, $(C_1-C_6)alkyl$, $[(C_1-C_6)alkyl]-C(=O)-$, $[(C_1-C_6)alkoxy]-C(=O)-$ and $[(C_1-C_6)alkyl]-SO_2-$; or

R^{Y1} and R^{Y2} taken together with the carbon atom to which they are attached form spiropyrrolidinyll or spiropiperidinyll, both of which are optionally N-substituted with a substituent selected from $(C_1-C_6)alkyl$, $(C_1-C_6)alkyl-C(=O)-$, $[(C_1-C_6)alkyl]-C(=O)-(C_1-C_6)alkyl$ and aryl- $C(=O)-$ wherein aryl is selected from phenyl and naphthyl;

R^{Y3} is hydrogen;

R^{Y4} is selected from hydroxy; $(C_1-C_6)alkyl$ optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, $[(C_1-$

C_6 alkyl]-C(=O)-, (C_1-C_6) alkoxy, $[(C_1-C_6)alkoxy]-C(=O)-$, $R^{a1}R^{a2}N-$ and $R^{a3}R^{a4}N-C(=O)-$, wherein R^{a1} , R^{a2} , R^{a3} and R^{a4} are independently selected from hydrogen, (C_1-C_6) alkyl, $[(C_1-C_6)alkyl]-C(=O)-$, $[(C_1-C_6)alkoxy]-C(=O)-$ and $[(C_1-C_6)alkyl]-SO_2-$; and (C_1-C_6) alkoxy optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, $[(C_1-C_6)alkyl]-C(=O)-$, (C_1-C_6) alkoxy, $[(C_1-C_6)alkoxy]-C(=O)-$, $R^{a5}R^{a6}N-$ and $R^{a7}R^{a8}N-C(=O)-$, wherein R^{a5} , R^{a6} , R^{a7} and R^{a8} are independently selected from hydrogen, (C_1-C_6) alkyl, $[(C_1-C_6)alkyl]-C(=O)-$, $[(C_1-C_6)alkoxy]-C(=O)-$ and $[(C_1-C_6)alkyl]-SO_2-$; and

R^{Y6} and R^{Y7} are independently selected from hydrogen; (C_1-C_6) alkyl optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, $[(C_1-C_6)alkyl]-C(=O)-$, (C_1-C_6) alkoxy, $[(C_1-C_6)alkoxy]-C(=O)-$, $R^{a1}R^{a2}N-$ and $R^{a3}R^{a4}N-C(=O)-$, wherein R^{a1} , R^{a2} , R^{a3} and R^{a4} are independently selected from hydrogen, (C_1-C_6) alkyl, $[(C_1-C_6)alkyl]-C(=O)-$, $[(C_1-C_6)alkoxy]-C(=O)-$ and $[(C_1-C_6)alkyl]-SO_2-$; heterocyclyl- $(CH_2)_{n6}-$ wherein $n6$ is an integer selected from 0, 1, 2, 3 and 4 and said heterocyclyl is four to eight membered containing one to three hetero atoms independently selected from nitrogen, oxygen and sulfur, wherein said heterocyclyl is optionally substituted with one to three substituents independently selected from hydroxy; (C_1-C_6) alkyl; $NH_2-C(=O)-$; $(C_1-C_6)alkyl-NH-C(=O)-$; $[(C_1-C_6)alkyl]_2-N-C(=O)-$; and non-, mono- and di-substituted amino wherein the substituents are independently selected from (C_1-C_6) alkyl, $[(C_1-C_6)alkyl]-C(=O)-$, $[(C_1-C_6)alkoxy]-C(=O)-$ and $[(C_1-C_6)alkyl]-SO_2-$; and heteroaryl- $(CH_2)_{n7}-$ wherein $n7$ is an integer selected from 0, 1, 2, 3 and 4 and said heteroaryl is five to ten membered containing one to three hetero atoms independently selected from nitrogen, oxygen and sulfur, wherein said heteroaryl is optionally substituted with one to three substituents independently selected from hydroxy; (C_1-C_6) alkyl; $NH_2-C(=O)-$; $(C_1-C_6)alkyl-NH-C(=O)-$; $[(C_1-C_6)alkyl]_2-N-C(=O)-$; and non-, mono- and di-substituted amino wherein the substituents are independently selected from (C_1-C_6) alkyl, $[(C_1-C_6)alkyl]-C(=O)-$, $[(C_1-C_6)alkoxy]-C(=O)-$ and $[(C_1-C_6)alkyl]-SO_2-$; or

R^{Y6} and R^{Y7} taken together with the nitrogen atom to which they are attached

form a four to eight heterocyclyl optionally containing, in addition to the nitrogen atom, one to two additional hetero atoms independently selected from nitrogen, oxygen and sulfur, and said heterocyclyl is optionally substituted with one substituent selected from hydroxy; (C₁-C₆)alkyl; NH₂-C(O=)-; (C₁-C₆)alkyl-NH-C(=O)-; [(C₁-C₆)alkyl]₂-N-C(=O)-; and non-, mono- and di-substituted amino wherein the substituents are independently selected from (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-;

said A is optionally substituted in the fused benzene rings with one to four substituents independently selected from halo; hydroxy; mercapto; phenyl; (C₁-C₆)alkyl optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, [(C₁-C₆)alkyl]-C(=O)-, (C₁-C₆)alkoxy, [(C₁-C₆)alkoxy]-C(=O)-, R^{a1}R^{a2}N- and R^{a3}R^{a4}N-C(=O)-, wherein R^{a1}, R^{a2}, R^{a3} and R^{a4} are independently selected from hydrogen, (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-; and (C₁-C₆)alkoxy optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, [(C₁-C₆)alkyl]-C(=O)-, (C₁-C₆)alkoxy, [(C₁-C₆)alkoxy]-C(=O)-, R^{a5}R^{a6}N- and R^{a7}R^{a8}N-C(=O)-, wherein R^{a5}, R^{a6}, R^{a7} and R^{a8} are independently selected from hydrogen, (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-; and

Z is C(=O).

Individual preferred compounds of this invention include

2,3-dihydro-1'-[3-(2-methoxycarbonylindolin-1-yl)-3-oxopropyl]spiro[1*H*-indene-1,4'-piperidine];

2,3-dihydro-1'-[3-(indolin-1-yl)-3-oxopropyl]spiro[1*H*-indene-1,4'-piperidine];

2,3-dihydro-1'-[3-(2-(S)-methoxycarbonylindolin-1-yl)-3-oxopropyl]spiro[1*H*-indene-1,4'-piperidine];

2,3-dihydro-1'-indolyl-3-oxopropylspiro[1*H*-indene-1,4'-piperidine];

2,3-dihydro-1'-[3-(2-hydroxymethylindolin-1-yl)-3-oxopropyl]spiro[1*H*-indene-1,4'-piperidine]; and

2,3-dihydro-1'-[3-(2-methoxymethylindolin-1-yl)-3-oxopropyl]spiro[1*H*-indene-1,4'-piperidine], or a salt thereof.

- Another preferred class of compound of formula (I) is that wherein
- all R^1 are hydrogen
- each R^2 is independently selected from hydrogen and halo;
- 5 X^1 is selected from $(CH_2)_{n1}$ wherein $n1$ is an integer selected from 1, 2 and 3; O; NH; S; C(=O); SO_2 ; and $N[(C_1-C_4)alkyl]$;
- X^2 is selected from CH_2 ; O; NH; S; C(=O); SO_2 ; and $N[(C_1-C_4)alkyl]$; or
- X^1 and X^2 taken together form $CH=CH$;
- W^1 and W^2 are both CH_2 ;
- 10 A is AB wherein
- Y^b is selected from C(=O); $CR^{Y1}R^{Y2}$; $CR^{Y3}[C(=O)R^{Y4}]$; $CR^{Y3}[NR^{Y5}C(=O)R^{Y4}]$; $CR^{Y3}[C(=O)NR^{Y6}R^{Y7}]$; and $CR^{Y3}[NR^{Y6}R^{Y7}]$;
- Y^c is selected from O; S; SO_2 ; NH; $N[(C_1-C_6)alkyl]$ wherein said $(C_1-C_6)alkyl$ is optionally substituted with one to three substituents independently selected from halo,
- 15 hydroxy, carboxy, $[(C_1-C_6)alkyl]-C(=O)-$, $(C_1-C_6)alkoxy$, $[(C_1-C_6)alkoxy]-C(=O)-$, $R^{a1}R^{a2}N-$ and $R^{a3}R^{a4}N-C(=O)-$, wherein R^{a1} , R^{a2} , R^{a3} and R^{a4} are independently selected from hydrogen, $(C_1-C_6)alkyl$, $[(C_1-C_6)alkyl]-C(=O)-$, $[(C_1-C_6)alkoxy]-C(=O)-$ and $[(C_1-C_6)alkyl]-SO_2-$; $N-(CH_2)_{n3}$ -heterocyclyl wherein $n3$ is an integer selected from 0, 1, 2 and 3, and said heterocyclyl contains from four to eight ring atoms one or two of
- 20 which are independently selected from nitrogen, oxygen and sulfur; $N-(CH_2)_{n4}$ -aryl wherein $n4$ is an integer selected from 0, 1, 2 and 3, and said aryl is selected from phenyl and naphthyl; and $N-(CH_2)_{n5}$ -heteroaryl wherein $n5$ is an integer selected from 0, 1, 2 and 3, and said heteroaryl is a five to ten membered aromatic heterocyclyl containing from one to four hetero atoms independently selected from nitrogen,
- 25 oxygen and sulfur; wherein
- R^{Y1} and R^{Y2} are independently selected from hydrogen; hydroxy; non-, mono- and di-substituted amino wherein the substituents are independently selected from $(C_1-C_6)alkyl$; $[(C_1-C_6)alkyl]-C(=O)-$; $[(C_1-C_6)alkoxy]-C(=O)-$; $[(C_1-C_6)alkyl]-SO_2-$; and four- to eight-membered heterocyclyl containing one to
- 30 four hetero atoms independently selected from nitrogen, oxygen and sulfur, wherein said heterocyclyl is optionally substituted with one to three substituents independently selected from hydroxy, $(C_1-C_6)alkyl$, $NH_2-C(O=)-$,

$[(C_1-C_6)alkyl]-NH-C(=O)-$, $[(C_1-C_6)alkyl]_2-N-C(=O)-$, and non-, mono- and di-substituted amino wherein the substituents are independently selected from $(C_1-C_6)alkyl$, $[(C_1-C_6)alkyl]-C(=O)-$, $[(C_1-C_6)alkoxy]-C(=O)-$ and $[(C_1-C_6)alkyl]-SO_2-$; $(C_1-C_6)alkyl$ optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, $[(C_1-C_6)alkyl]-C(=O)-$, $(C_1-C_6)alkoxy$, $[(C_1-C_6)alkoxy]-C(=O)-$, $R^{a1}R^{a2}N-$ and $R^{a3}R^{a4}N-C(=O)-$, wherein R^{a1} , R^{a2} , R^{a3} and R^{a4} are independently selected from hydrogen, $(C_1-C_6)alkyl$, $[(C_1-C_6)alkyl]-C(=O)-$, $[(C_1-C_6)alkoxy]-C(=O)-$ and $[(C_1-C_6)alkyl]-SO_2-$; and $(C_1-C_6)alkoxy$ optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, $[(C_1-C_6)alkyl]-C(=O)-$, $(C_1-C_6)alkoxy$, $[(C_1-C_6)alkoxy]-C(=O)-$, $R^{a5}R^{a6}N-$ and $R^{a7}R^{a8}N-C(=O)-$, wherein R^{a5} , R^{a6} , R^{a7} and R^{a8} are independently selected from hydrogen, $(C_1-C_6)alkyl$, $[(C_1-C_6)alkyl]-C(=O)-$, $[(C_1-C_6)alkoxy]-C(=O)-$ and $[(C_1-C_6)alkyl]-SO_2-$; or

R^{Y1} and R^{Y2} taken together with the carbon atom to which they are attached form spiropyrrolidinyl or spiropiperidinyl, both of which are optionally N-substituted with a substituent selected from $(C_1-C_6)alkyl$, $(C_1-C_6)alkyl-C(=O)-$, $[(C_1-C_6)alkyl]-C(=O)-(C_1-C_6)alkyl$ and aryl- $C(=O)-$ wherein aryl is selected from phenyl and naphthyl;

R^{Y3} is hydrogen;

R^{Y4} is selected from hydroxy; $(C_1-C_6)alkyl$ optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, $[(C_1-C_6)alkyl]-C(=O)-$, $(C_1-C_6)alkoxy$, $[(C_1-C_6)alkoxy]-C(=O)-$, $R^{a1}R^{a2}N-$ and $R^{a3}R^{a4}N-C(=O)-$, wherein R^{a1} , R^{a2} , R^{a3} and R^{a4} are independently selected from hydrogen, $(C_1-C_6)alkyl$, $[(C_1-C_6)alkyl]-C(=O)-$, $[(C_1-C_6)alkoxy]-C(=O)-$ and $[(C_1-C_6)alkyl]-SO_2-$; and $(C_1-C_6)alkoxy$ optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, $[(C_1-C_6)alkyl]-C(=O)-$, $(C_1-C_6)alkoxy$, $[(C_1-C_6)alkoxy]-C(=O)-$, $R^{a5}R^{a6}N-$ and $R^{a7}R^{a8}N-C(=O)-$, wherein R^{a5} , R^{a6} , R^{a7} and R^{a8} are independently selected from hydrogen, $(C_1-C_6)alkyl$, $[(C_1-C_6)alkyl]-C(=O)-$, $[(C_1-C_6)alkoxy]-C(=O)-$ and $[(C_1-C_6)alkyl]-SO_2-$; and

R^{Y5} , R^{Y6} and R^{Y7} are independently selected from hydrogen; $(C_1-C_6)alkyl$

optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, [(C₁-C₆)alkyl]-C(=O)-, (C₁-C₆)alkoxy, [(C₁-C₆)alkoxy]-C(=O)-, R^{a1}R^{a2}N- and R^{a3}R^{a4}N-C(=O)-, wherein R^{a1}, R^{a2}, R^{a3} and R^{a4} are independently selected from hydrogen, (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-; heterocyclyl-(CH₂)_{n6}- wherein n₆ is an integer selected from 0, 1, 2, 3 and 4 and said heterocyclyl is four to eight membered containing one to three hetero atoms independently selected from nitrogen, oxygen and sulfur, wherein said heterocyclyl is optionally substituted with one to three substituents independently selected from hydroxy; (C₁-C₆)alkyl; NH₂-C(=O)-; (C₁-C₆)alkyl-NH-C(=O)-; [(C₁-C₆)alkyl]₂-N-C(=O)-; and non-, mono- and di-substituted amino wherein the substituents are independently selected from (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-; and

heteroaryl-(CH₂)_{n7}- wherein n₇ is an integer selected from 0, 1, 2, 3 and 4 and said heteroaryl is five to ten membered containing one to three hetero atoms independently selected from nitrogen, oxygen and sulfur, wherein said heteroaryl is optionally substituted with one to three substituents independently selected from hydroxy; (C₁-C₆)alkyl; NH₂-C(=O)-; (C₁-C₆)alkyl-NH-C(=O)-; [(C₁-C₆)alkyl]₂-N-C(=O)-; and non-, mono- and di-substituted amino wherein the substituents are independently selected from (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-; or

R^{Y6} and R^{Y7} taken together with the nitrogen atom to which they are attached form a four to eight heterocyclyl optionally containing, in addition to the nitrogen atom, one to two additional hetero atoms independently selected from nitrogen, oxygen and sulfur, and said heterocyclyl is optionally substituted with one substituent selected from hydroxy; (C₁-C₆)alkyl; NH₂-C(=O)-; (C₁-C₆)alkyl-NH-C(=O)-; [(C₁-C₆)alkyl]₂-N-C(=O)-; and non-, mono- and di-substituted amino wherein the substituents are independently selected from (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-;

said A is optionally substituted in the fused benzene rings with one to four substituents

independently selected from halo; hydroxy; mercapto; phenyl; (C₁-C₆)alkyl optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, [(C₁-C₆)alkyl]-C(=O)-, (C₁-C₆)alkoxy, [(C₁-C₆)alkoxy]-C(=O)-, R^{a1}R^{a2}N- and R^{a3}R^{a4}N-C(=O)-, wherein R^{a1}, R^{a2}, R^{a3} and R^{a4} are independently selected from hydrogen, (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-; and (C₁-C₆)alkoxy optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, [(C₁-C₆)alkyl]-C(=O)-, (C₁-C₆)alkoxy, [(C₁-C₆)alkoxy]-C(=O)-, R^{a5}R^{a6}N- and R^{a7}R^{a8}N-C(=O)-, wherein R^{a5}, R^{a6}, R^{a7} and R^{a8} are independently selected from hydrogen, (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-; and Z is selected from C(=O); (CH₂)_{n8} wherein n8 is an integer selected from 0, 1 and 2; and CHR^{Z1} wherein

R^{Z1} is selected from carboxy; (C₁-C₆)alkoxy-C(=O)-; non-, mono- and di-substituted amino wherein the substituents are independently selected from (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkyl]-C(=O)-O- and [(C₁-C₆)alkyl]-SO₂-; (C₁-C₆)alkyl optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, [(C₁-C₆)alkyl]-C(=O)-, (C₁-C₆)alkoxy, [(C₁-C₆)alkoxy]-C(=O)-, R^{a1}R^{a2}N- and R^{a3}R^{a4}N-C(=O)-, wherein R^{a1}, R^{a2}, R^{a3} and R^{a4} are independently selected from hydrogen, (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-; and [C(=O)-NR^{Z11}R^{Z12}] wherein R^{Z11} and R^{Z12} are independently selected from hydrogen and (C₁-C₆)alkyl optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, [(C₁-C₆)alkyl]-C(=O)-, (C₁-C₆)alkoxy, [(C₁-C₆)alkoxy]-C(=O)-, R^{a1}R^{a2}N- and R^{a3}R^{a4}N-C(=O)-, wherein R^{a1}, R^{a2}, R^{a3} and R^{a4} are independently selected from hydrogen, (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-.

Individual preferred compounds of this invention include

2,3-dihydro-1'-[3-(benzimidazol-2-one-1-yl)propyl]spiro[1*H*-indene-1,4'-piperidine];
 2,3-dihydro-1'-[3-(benzothiazol-2-one-1-yl)propyl]spiro[1*H*-indene-1,4'-piperidine];
 2,3-dihydro-1'-[3-(2-oxo-1,3-benzoxazol-3(2*H*)-yl)propyl]spiro[1*H*-indene-1,4'-piperidine];

2,3-dihydro-1'-[3-(2-hydroxymethylbenzimidazol-1-yl)-3-oxopropyl]spiro[1*H*-indene-1,4'-piperidine];

2,3-dihydro-1'-[3-(3-ethylbenzimidazol-2-one-1-yl)propyl]spiro[1*H*-indene-1,4'-piperidine];

5 2,3-dihydro-1'-[3-(2-acetamidobenzimidazol-1-yl)propyl]spiro[1*H*-indene-1,4'-piperidine];

2,3-dihydro-1'-{3-[3-(2-hydroxyethyl)benzimidazol-2-one-1-yl)propyl]spiro[1*H*-indene-1,4'-piperidine];

2,3-dihydro-1'-{3-[3-(2-aminoethyl)benzimidazol-2-one-1-yl)propyl]spiro[1*H*-indene-1,4'-piperidine]; and

2,3-dihydro-1'-{3-[3-(2-acetamidoethyl)benzimidazol-2-one-1-yl)propyl]spiro[1*H*-indene-1,4'-piperidine], or a salt thereof.

Another preferred class of compound of formula (I) of this invention is that

15 wherein

all R¹ are hydrogen

each R² is independently selected from hydrogen and halo;

X¹ is selected from (CH₂)_{n1} wherein n1 is an integer selected from 1, 2 and 3; O; NH; S; C(=O); SO₂; and N[(C₁-C₄)alkyl];

20 X² is selected from CH₂; O; NH; S; C(=O); SO₂; and N[(C₁-C₄)alkyl]; or

X¹ and X² taken together form CH=CH;

W¹ and W² are independently selected from CR^{W1}R^{W2},

wherein

25 R^{W1} and R^{W2} are independently selected from hydrogen; halo; hydroxy; (C₁-C₆)alkyl optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, [(C₁-C₆)alkyl]-C(=O)-, (C₁-C₆)alkoxy, [(C₁-C₆)alkoxy]-C(=O)-, R^{a1}R^{a2}N- and R^{a3}R^{a4}N-C(=O)-, wherein R^{a1}, R^{a2}, R^{a3} and R^{a4} are independently selected from hydrogen, (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-; (C₁-C₆)alkoxy optionally substituted with one to three substituents independently selected from halo,

30 hydroxy, carboxy, [(C₁-C₆)alkyl]-C(=O)-, (C₁-C₆)alkoxy, [(C₁-C₆)alkoxy]-C(=O)-,

$R^{a5}R^{a6}N-$ and $R^{a7}R^{a8}N-C(=O)-$, wherein R^{a5} , R^{a6} , R^{a7} and R^{a8} are independently selected from hydrogen, $(C_1-C_6)alkyl$, $[(C_1-C_6)alkyl]-C(=O)-$, $[(C_1-C_6)alkoxy]-C(=O)-$ and $[(C_1-C_6)alkyl]-SO_2-$; $C(=O)-[(C_1-C_6)alkyl]$ wherein said $(C_1-C_6)alkyl$ is optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, $[(C_1-C_6)alkyl]-C(=O)-$, $(C_1-C_6)alkoxy$, $[(C_1-C_6)alkoxy]-C(=O)-$, $R^{a1}R^{a2}N-$ and $R^{a3}R^{a4}N-C(=O)-$, wherein R^{a1} , R^{a2} , R^{a3} and R^{a4} are independently selected from hydrogen, $(C_1-C_6)alkyl$, $[(C_1-C_6)alkyl]-C(=O)-$, $[(C_1-C_6)alkoxy]-C(=O)-$ and $[(C_1-C_6)alkyl]-SO_2-$; $C(=O)-NR^{w11}R^{w12}$ wherein R^{w11} and R^{w12} are independently selected from hydrogen and $(C_1-C_6)alkyl$ optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, $[(C_1-C_6)alkyl]-C(=O)-$, $(C_1-C_6)alkoxy$, $[(C_1-C_6)alkoxy]-C(=O)-$, $R^{a1}R^{a2}N-$ and $R^{a3}R^{a4}N-C(=O)-$, wherein R^{a1} , R^{a2} , R^{a3} and R^{a4} are independently selected from hydrogen, $(C_1-C_6)alkyl$, $[(C_1-C_6)alkyl]-C(=O)-$, $[(C_1-C_6)alkoxy]-C(=O)-$ and $[(C_1-C_6)alkyl]-SO_2-$; $NR^{w13}R^{w14}$ wherein R^{w13} and R^{w14} are independently selected from hydrogen and $(C_1-C_6)alkyl$ optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, $[(C_1-C_6)alkyl]-C(=O)-$, $(C_1-C_6)alkoxy$, $[(C_1-C_6)alkoxy]-C(=O)-$, $R^{a1}R^{a2}N-$ and $R^{a3}R^{a4}N-C(=O)-$, wherein R^{a1} , R^{a2} , R^{a3} and R^{a4} are independently selected from hydrogen, $(C_1-C_6)alkyl$, $[(C_1-C_6)alkyl]-C(=O)-$, $[(C_1-C_6)alkoxy]-C(=O)-$ and $[(C_1-C_6)alkyl]-SO_2-$; aryl selected from phenyl and naphthyl; and four- to eight-membered heterocyclyl containing one to four hetero atoms independently selected from nitrogen, oxygen and sulfur;

A is AC wherein

Y^d , Y^e and Y^f are independently selected from $C(=O)$; $CR^{y1}R^{y2}$; $CR^{y3}[C(=O)R^{y4}]$; $CR^{y3}[NR^{y5}C(=O)R^{y4}]$; $CR^{y3}[C(=O)NR^{y6}R^{y7}]$; $CR^{y3}[NR^{y6}R^{y7}]$; O; S; SO_2 ; NH; $N[(C_1-C_6)alkyl]$ wherein said $(C_1-C_6)alkyl$ is optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, $[(C_1-C_6)alkyl]-C(=O)-$, $(C_1-C_6)alkoxy$, $[(C_1-C_6)alkoxy]-C(=O)-$, $R^{a1}R^{a2}N-$ and $R^{a3}R^{a4}N-C(=O)-$, wherein R^{a1} , R^{a2} , R^{a3} and R^{a4} are independently selected from hydrogen, $(C_1-C_6)alkyl$, $[(C_1-C_6)alkyl]-C(=O)-$, $[(C_1-C_6)alkoxy]-C(=O)-$ and $[(C_1-C_6)alkyl]-SO_2-$; $N-(CH_2)_{n3}$ -heterocyclyl wherein $n3$ is an integer selected from 0, 1, 2 and 3, and said heterocyclyl contains from four to eight ring atoms one or two of which

are independently selected from nitrogen, oxygen and sulfur; $N-(CH_2)_{n4}$ -aryl wherein $n4$ is an integer selected from 0, 1, 2 and 3, and said aryl is selected from phenyl and naphthyl; and $N-(CH_2)_{n5}$ -heteroaryl wherein $n5$ is an integer selected from 0, 1, 2 and 3, and said heteroaryl is a five to ten membered aromatic heterocyclyl containing from one to four hetero atoms independently selected from nitrogen, oxygen and sulfur;

R^{Y1} and R^{Y2} are independently selected from hydrogen; hydroxy; non-, mono- and di-substituted amino wherein the substituents are independently selected from (C_1-C_6) alkyl; $[(C_1-C_6)alkyl]-C(=O)-$; $[(C_1-C_6)alkoxy]-C(=O)-$; $[(C_1-C_6)alkyl]-SO_2-$; and four- to eight-membered heterocyclyl containing one to four hetero atoms independently selected from nitrogen, oxygen and sulfur, wherein said heterocyclyl is optionally substituted with one to three substituents independently selected from hydroxy, $(C_1-C_6)alkyl$, $NH_2-C(=O)-$, $[(C_1-C_6)alkyl]-NH-C(=O)-$, $[(C_1-C_6)alkyl]_2-N-C(=O)-$, and non-, mono- and di-substituted amino wherein the substituents are independently selected from $(C_1-C_6)alkyl$, $[(C_1-C_6)alkyl]-C(=O)-$, $[(C_1-C_6)alkoxy]-C(=O)-$ and $[(C_1-C_6)alkyl]-SO_2-$; $(C_1-C_6)alkyl$ optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, $[(C_1-C_6)alkyl]-C(=O)-$, $(C_1-C_6)alkoxy$, $[(C_1-C_6)alkoxy]-C(=O)-$, $R^{a1}R^{a2}N-$ and $R^{a3}R^{a4}N-C(=O)-$, wherein R^{a1} , R^{a2} , R^{a3} and R^{a4} are independently selected from hydrogen, $(C_1-C_6)alkyl$, $[(C_1-C_6)alkyl]-C(=O)-$, $[(C_1-C_6)alkoxy]-C(=O)-$ and $[(C_1-C_6)alkyl]-SO_2-$; and $(C_1-C_6)alkoxy$ optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, $[(C_1-C_6)alkyl]-C(=O)-$, $(C_1-C_6)alkoxy$, $[(C_1-C_6)alkoxy]-C(=O)-$, $R^{a5}R^{a6}N-$ and $R^{a7}R^{a8}N-C(=O)-$, wherein R^{a5} , R^{a6} , R^{a7} and R^{a8} are independently selected from hydrogen, $(C_1-C_6)alkyl$, $[(C_1-C_6)alkyl]-C(=O)-$, $[(C_1-C_6)alkoxy]-C(=O)-$ and $[(C_1-C_6)alkyl]-SO_2-$; or

R^{Y1} and R^{Y2} taken together with the carbon atom to which they are attached form spiropyrrolidinyl or spiropiperidinyl, both of which are optionally N-substituted with a substituent selected from $(C_1-C_6)alkyl$, $(C_1-C_6)alkyl-C(=O)-$, $[(C_1-C_6)alkyl]-C(=O)-(C_1-C_6)alkyl$ and $aryl-C(=O)-$ wherein aryl is selected from phenyl and naphthyl;

R^{Y3} is hydrogen;

R^{Y4} is selected from hydroxy; (C_1-C_6) alkyl optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, $[(C_1-C_6)alkyl]-C(=O)-$, $(C_1-C_6)alkoxy$, $[(C_1-C_6)alkoxy]-C(=O)-$, $R^{a1}R^{a2}N-$ and $R^{a3}R^{a4}N-C(=O)-$, wherein R^{a1} , R^{a2} , R^{a3} and R^{a4} are independently selected from hydrogen, $(C_1-C_6)alkyl$, $[(C_1-C_6)alkyl]-C(=O)-$, $[(C_1-C_6)alkoxy]-C(=O)-$ and $[(C_1-C_6)alkyl]-SO_2-$; and $(C_1-C_6)alkoxy$ optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, $[(C_1-C_6)alkyl]-C(=O)-$, $(C_1-C_6)alkoxy$, $[(C_1-C_6)alkoxy]-C(=O)-$, $R^{a5}R^{a6}N-$ and $R^{a7}R^{a8}N-C(=O)-$, wherein R^{a5} , R^{a6} , R^{a7} and R^{a8} are independently selected from hydrogen, $(C_1-C_6)alkyl$, $[(C_1-C_6)alkyl]-C(=O)-$, $[(C_1-C_6)alkoxy]-C(=O)-$ and $[(C_1-C_6)alkyl]-SO_2-$; and

R^{Y5} , R^{Y6} and R^{Y7} are independently selected from hydrogen; $(C_1-C_6)alkyl$ optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, $[(C_1-C_6)alkyl]-C(=O)-$, $(C_1-C_6)alkoxy$, $[(C_1-C_6)alkoxy]-C(=O)-$, $R^{a1}R^{a2}N-$ and $R^{a3}R^{a4}N-C(=O)-$, wherein R^{a1} , R^{a2} , R^{a3} and R^{a4} are independently selected from hydrogen, $(C_1-C_6)alkyl$, $[(C_1-C_6)alkyl]-C(=O)-$, $[(C_1-C_6)alkoxy]-C(=O)-$ and $[(C_1-C_6)alkyl]-SO_2-$; heterocyclyl- $(CH_2)_{n6}-$ wherein $n6$ is an integer selected from 0, 1, 2, 3 and 4 and said heterocyclyl is four to eight membered containing one to three hetero atoms independently selected from nitrogen, oxygen and sulfur, wherein said heterocyclyl is optionally substituted with one to three substituents independently selected from hydroxy; $(C_1-C_6)alkyl$; $NH_2-C(=O)-$; $(C_1-C_6)alkyl-NH-C(=O)-$; $[(C_1-C_6)alkyl]_2-N-C(=O)-$; and non-, mono- and di-substituted amino wherein the substituents are independently selected from $(C_1-C_6)alkyl$, $[(C_1-C_6)alkyl]-C(=O)-$, $[(C_1-C_6)alkoxy]-C(=O)-$ and $[(C_1-C_6)alkyl]-SO_2-$; and heteroaryl- $(CH_2)_{n7}-$ wherein $n7$ is an integer selected from 0, 1, 2, 3 and 4 and said heteroaryl is five to ten membered containing one to three hetero atoms independently selected from nitrogen, oxygen and sulfur, wherein said heteroaryl is optionally substituted with one to three substituents independently selected from hydroxy; $(C_1-C_6)alkyl$; $NH_2-C(=O)-$; $(C_1-C_6)alkyl-NH-C(=O)-$; $[(C_1-C_6)alkyl]_2-N-C(=O)-$; and non-, mono- and di-substituted amino wherein the substituents are

independently selected from (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-; or

R^{Y6} and R^{Y7} taken together with the nitrogen atom to which they are attached form a four to eight heterocyclyl optionally containing, in addition to the nitrogen atom, one to two additional hetero atoms independently selected from nitrogen, oxygen and sulfur, and said heterocyclyl is optionally substituted with one substituent selected from hydroxy; (C₁-C₆)alkyl; NH₂-C(O=)-; (C₁-C₆)alkyl-NH-C(=O)-; [(C₁-C₆)alkyl]₂-N-C(=O)-; and non-, mono- and di-substituted amino wherein the substituents are independently selected from (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-; and

said A is optionally substituted in the fused benzene rings with one to four substituents independently selected from halo; hydroxy; mercapto; phenyl; (C₁-C₆)alkyl optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, [(C₁-C₆)alkyl]-C(=O)-, (C₁-C₆)alkoxy, [(C₁-C₆)alkoxy]-C(=O)-, R^{a1}R^{a2}N- and R^{a3}R^{a4}N-C(=O)-, wherein R^{a1}, R^{a2}, R^{a3} and R^{a4} are independently selected from hydrogen, (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-; and (C₁-C₆)alkoxy optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, [(C₁-C₆)alkyl]-C(=O)-, (C₁-C₆)alkoxy, [(C₁-C₆)alkoxy]-C(=O)-, R^{a5}R^{a6}N- and R^{a7}R^{a8}N-C(=O)-, wherein R^{a5}, R^{a6}, R^{a7} and R^{a8} are independently selected from hydrogen, (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-; and Z is selected from C(=O); (CH₂)_{n8} wherein n8 is an integer selected from 0, 1 and 2; and CHR^{Z1} wherein

R^{Z1} is selected from carboxy; (C₁-C₆)alkoxy-C(=O)-; non-, mono- and di-substituted amino wherein the substituents are independently selected from (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkyl]-C(=O)-O- and [(C₁-C₆)alkyl]-SO₂-; (C₁-C₆)alkyl optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, [(C₁-C₆)alkyl]-C(=O)-, (C₁-C₆)alkoxy, [(C₁-C₆)alkoxy]-C(=O)-, R^{a1}R^{a2}N- and R^{a3}R^{a4}N-C(=O)-, wherein R^{a1}, R^{a2}, R^{a3} and R^{a4} are independently selected from hydrogen, (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-; and

[C(=O)-NR^{Z11}R^{Z12}] wherein R^{Z11} and R^{Z12} are independently selected from hydrogen and (C₁-C₆)alkyl optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, [(C₁-C₆)alkyl]-C(=O)-, (C₁-C₆)alkoxy, [(C₁-C₆)alkoxy]-C(=O)-, R^{a1}R^{a2}N- and R^{a3}R^{a4}N-C(=O)-, wherein R^{a1}, R^{a2}, R^{a3} and R^{a4} are independently selected from hydrogen, (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-.

Individual preferred compounds of this invention include 2,3-dihydro-1'-[3-(2-oxo-3,4-dihydro-1(2*H*)-quinoliny)propyl]spiro[1*H*-indene-1,4'-piperidine] and 2,3-dihydro-1'-[3-(3-methyl-2-oxo-3,4-dihydro-1(2*H*)-quinazoliny)propyl]spiro[1*H*-indene-1,4'-piperidine]; or a salt thereof.

Another preferred class of compound of formula (I) of this invention is that wherein

all R¹ are hydrogen

each R² is independently selected from hydrogen and halo;

X¹ is selected from (CH₂)_{n1} wherein n1 is an integer selected from 1, 2 and 3; O; NH; S; C(=O); SO₂; and N[(C₁-C₄)alkyl];

X² is selected from CH₂; O; NH; S; C(=O); SO₂; and N[(C₁-C₄)alkyl]; or

X¹ and X² taken together form CH=CH;

W¹ and W² are independently selected from CR^{W1}R^{W2},

wherein

R^{W1} and R^{W2} are independently selected from hydrogen; halo; hydroxy; (C₁-C₆)alkyl optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, [(C₁-C₆)alkyl]-C(=O)-, (C₁-C₆)alkoxy, [(C₁-C₆)alkoxy]-C(=O)-, R^{a1}R^{a2}N- and R^{a3}R^{a4}N-C(=O)-, wherein R^{a1}, R^{a2}, R^{a3} and R^{a4} are independently selected from hydrogen, (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-; (C₁-C₆)alkoxy optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, [(C₁-C₆)alkyl]-C(=O)-, (C₁-C₆)alkoxy, [(C₁-C₆)alkoxy]-C(=O)-, R^{a5}R^{a6}N- and R^{a7}R^{a8}N-C(=O)-, wherein R^{a5}, R^{a6}, R^{a7} and R^{a8} are independently selected from hydrogen, (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-

$C(=O)-$ and $[(C_1-C_6)alkyl]-SO_2-$; $C(=O)-[(C_1-C_6)alkyl]$ wherein said $(C_1-C_6)alkyl$ is optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, $[(C_1-C_6)alkyl]-C(=O)-$, $(C_1-C_6)alkoxy$, $[(C_1-C_6)alkoxy]-C(=O)-$, $R^{a1}R^{a2}N-$ and $R^{a3}R^{a4}N-C(=O)-$, wherein R^{a1} , R^{a2} , R^{a3} and R^{a4} are independently selected from hydrogen, $(C_1-C_6)alkyl$, $[(C_1-C_6)alkyl]-C(=O)-$, $[(C_1-C_6)alkoxy]-C(=O)-$ and $[(C_1-C_6)alkyl]-SO_2-$; $C(=O)-NR^{W11}R^{W12}$ wherein R^{W11} and R^{W12} are independently selected from hydrogen and $(C_1-C_6)alkyl$ optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, $[(C_1-C_6)alkyl]-C(=O)-$, $(C_1-C_6)alkoxy$, $[(C_1-C_6)alkoxy]-C(=O)-$, $R^{a1}R^{a2}N-$ and $R^{a3}R^{a4}N-C(=O)-$, wherein R^{a1} , R^{a2} , R^{a3} and R^{a4} are independently selected from hydrogen, $(C_1-C_6)alkyl$, $[(C_1-C_6)alkyl]-C(=O)-$, $[(C_1-C_6)alkoxy]-C(=O)-$ and $[(C_1-C_6)alkyl]-SO_2-$; $NR^{W13}R^{W14}$ wherein R^{W13} and R^{W14} are independently selected from hydrogen and $(C_1-C_6)alkyl$ optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, $[(C_1-C_6)alkyl]-C(=O)-$, $(C_1-C_6)alkoxy$, $[(C_1-C_6)alkoxy]-C(=O)-$, $R^{a1}R^{a2}N-$ and $R^{a3}R^{a4}N-C(=O)-$, wherein R^{a1} , R^{a2} , R^{a3} and R^{a4} are independently selected from hydrogen, $(C_1-C_6)alkyl$, $[(C_1-C_6)alkyl]-C(=O)-$, $[(C_1-C_6)alkoxy]-C(=O)-$ and $[(C_1-C_6)alkyl]-SO_2-$; aryl selected from phenyl and naphthyl; and four- to eight-membered heterocyclyl containing one to four hetero atoms independently selected from nitrogen, oxygen and sulfur;

A is AE wherein

Y^i , Y^j , Y^k and Y^m are independently selected from $C(=O)$; $CR^{Y1}R^{Y2}$; $CR^{Y3}[C(=O)R^{Y4}]$; $CR^{Y3}[NR^{Y5}C(=O)R^{Y4}]$; $CR^{Y3}[C(=O)NR^{Y6}R^{Y7}]$; $CR^{Y3}[NR^{Y6}R^{Y7}]$; O; S; SO_2 ; NH; $N[(C_1-C_6)alkyl]$ wherein said $(C_1-C_6)alkyl$ is optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, $[(C_1-C_6)alkyl]-C(=O)-$, $(C_1-C_6)alkoxy$, $[(C_1-C_6)alkoxy]-C(=O)-$, $R^{a1}R^{a2}N-$ and $R^{a3}R^{a4}N-C(=O)-$, wherein R^{a1} , R^{a2} , R^{a3} and R^{a4} are independently selected from hydrogen, $(C_1-C_6)alkyl$, $[(C_1-C_6)alkyl]-C(=O)-$, $[(C_1-C_6)alkoxy]-C(=O)-$ and $[(C_1-C_6)alkyl]-SO_2-$; $N-(CH_2)_{n3}$ -heterocyclyl wherein $n3$ is an integer selected from 0, 1, 2 and 3, and said heterocyclyl contains from four to eight ring atoms one or two of which are independently selected from nitrogen, oxygen and sulfur; $N-(CH_2)_{n4}$ -aryl wherein $n4$ is an integer selected from 0, 1, 2

and 3, and said aryl is selected from phenyl and naphthyl; and $N-(CH_2)_{n5}$ -heteroaryl wherein $n5$ is an integer selected from 0, 1, 2 and 3, and said heteroaryl is a five to ten membered aromatic heterocyclyl containing from one to four hetero atoms independently selected from nitrogen, oxygen and sulfur;

5 R^{Y1} and R^{Y2} are independently selected from hydrogen; hydroxy; non-, mono- and di-substituted amino wherein the substituents are independently selected from (C_1-C_6) alkyl; $[(C_1-C_6)alkyl]-C(=O)-$; $[(C_1-C_6)alkoxy]-C(=O)-$; $[(C_1-C_6)alkyl]-SO_2-$; and four- to eight-membered heterocyclyl containing one to four hetero atoms independently selected from nitrogen, oxygen and sulfur,
 10 wherein said heterocyclyl is optionally substituted with one to three substituents independently selected from hydroxy, (C_1-C_6) alkyl, $NH_2-C(=O)-$, $[(C_1-C_6)alkyl]-NH-C(=O)-$, $[(C_1-C_6)alkyl]_2-N-C(=O)-$, and non-, mono- and di-substituted amino wherein the substituents are independently selected from (C_1-C_6) alkyl, $[(C_1-C_6)alkyl]-C(=O)-$, $[(C_1-C_6)alkoxy]-C(=O)-$ and $[(C_1-C_6)alkyl]-SO_2-$;
 15 $(C_1-C_6)alkyl$ optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, $[(C_1-C_6)alkyl]-C(=O)-$, $(C_1-C_6)alkoxy$, $[(C_1-C_6)alkoxy]-C(=O)-$, $R^{a1}R^{a2}N-$ and $R^{a3}R^{a4}N-C(=O)-$, wherein R^{a1} , R^{a2} , R^{a3} and R^{a4} are independently selected from hydrogen, $(C_1-C_6)alkyl$, $[(C_1-C_6)alkyl]-C(=O)-$, $[(C_1-C_6)alkoxy]-C(=O)-$ and $[(C_1-C_6)alkyl]-SO_2-$;
 20 and $(C_1-C_6)alkoxy$ optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, $[(C_1-C_6)alkyl]-C(=O)-$, $(C_1-C_6)alkoxy$, $[(C_1-C_6)alkoxy]-C(=O)-$, $R^{a5}R^{a6}N-$ and $R^{a7}R^{a8}N-C(=O)-$, wherein R^{a5} , R^{a6} , R^{a7} and R^{a8} are independently selected from hydrogen, $(C_1-C_6)alkyl$, $[(C_1-C_6)alkyl]-C(=O)-$, $[(C_1-C_6)alkoxy]-C(=O)-$ and $[(C_1-C_6)alkyl]-SO_2-$; or
 25

R^{Y1} and R^{Y2} taken together with the carbon atom to which they are attached form spiropyrrolidinyll or spiropiperidinyll, both of which are optionally N-substituted with a substituent selected from $(C_1-C_6)alkyl$, $(C_1-C_6)alkyl-C(=O)-$, $[(C_1-C_6)alkyl]-C(=O)-(C_1-C_6)alkyl$ and $aryl-C(=O)-$ wherein aryl is selected from phenyl and naphthyl;
 30

R^{Y3} is hydrogen;

R^{Y4} is selected from hydroxy; $(C_1-C_6)alkyl$ optionally substituted with one to

three substituents independently selected from halo, hydroxy, carboxy, [(C₁-C₆)alkyl]-C(=O)-, (C₁-C₆)alkoxy, [(C₁-C₆)alkoxy]-C(=O)-, R^{a1}R^{a2}N- and R^{a3}R^{a4}N-C(=O)-, wherein R^{a1}, R^{a2}, R^{a3} and R^{a4} are independently selected from hydrogen, (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-; and (C₁-C₆)alkoxy optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, [(C₁-C₆)alkyl]-C(=O)-, (C₁-C₆)alkoxy, [(C₁-C₆)alkoxy]-C(=O)-, R^{a5}R^{a6}N- and R^{a7}R^{a8}N-C(=O)-, wherein R^{a5}, R^{a6}, R^{a7} and R^{a8} are independently selected from hydrogen, (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-; and

R^{Y5}, R^{Y6} and R^{Y7} are independently selected from hydrogen; (C₁-C₆)alkyl optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, [(C₁-C₆)alkyl]-C(=O)-, (C₁-C₆)alkoxy, [(C₁-C₆)alkoxy]-C(=O)-, R^{a1}R^{a2}N- and R^{a3}R^{a4}N-C(=O)-, wherein R^{a1}, R^{a2}, R^{a3} and R^{a4} are independently selected from hydrogen, (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-; heterocyclyl-(CH₂)_{n6}- wherein n₆ is an integer selected from 0, 1, 2, 3 and 4 and said heterocyclyl is four to eight membered containing one to three hetero atoms independently selected from nitrogen, oxygen and sulfur, wherein said heterocyclyl is optionally substituted with one to three substituents independently selected from hydroxy; (C₁-C₆)alkyl; NH₂-C(=O)-; (C₁-C₆)alkyl-NH-C(=O)-; [(C₁-C₆)alkyl]₂-N-C(=O)-; and non-, mono- and di-substituted amino wherein the substituents are independently selected from (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-; and heteroaryl-(CH₂)_{n7}- wherein n₇ is an integer selected from 0, 1, 2, 3 and 4 and said heteroaryl is five to ten membered containing one to three hetero atoms independently selected from nitrogen, oxygen and sulfur, wherein said heteroaryl is optionally substituted with one to three substituents independently selected from hydroxy; (C₁-C₆)alkyl; NH₂-C(=O)-; (C₁-C₆)alkyl-NH-C(=O)-; [(C₁-C₆)alkyl]₂-N-C(=O)-; and non-, mono- and di-substituted amino wherein the substituents are independently selected from (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-; or

5 R^{Y6} and R^{Y7} taken together with the nitrogen atom to which they are attached form a four to eight heterocyclyl optionally containing, in addition to the nitrogen atom, one to two additional hetero atoms independently selected from nitrogen, oxygen and sulfur, and said heterocyclyl is optionally substituted with one substituent selected from hydroxy; (C_1-C_6) alkyl; NH_2- $C(O=)-$; $(C_1-C_6)alkyl-NH-C(=O)-$; $[(C_1-C_6)alkyl]_2-N-C(=O)-$; and non-, mono- and di-substituted amino wherein the substituents are independently selected from $(C_1-C_6)alkyl$, $[(C_1-C_6)alkyl]-C(=O)-$, $[(C_1-C_6)alkoxy]-C(=O)-$ and $[(C_1-C_6)alkyl]-SO_2-$; and

10 said A is optionally substituted in the fused benzene rings with one to four substituents independently selected from halo; hydroxy; mercapto; phenyl; $(C_1-C_6)alkyl$ optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, $[(C_1-C_6)alkyl]-C(=O)-$, $(C_1-C_6)alkoxy$, $[(C_1-C_6)alkoxy]-C(=O)-$, $R^{a1}R^{a2}N-$ and $R^{a3}R^{a4}N-C(=O)-$, wherein R^{a1} , R^{a2} , R^{a3} and R^{a4} are independently selected from
 15 hydrogen, $(C_1-C_6)alkyl$, $[(C_1-C_6)alkyl]-C(=O)-$, $[(C_1-C_6)alkoxy]-C(=O)-$ and $[(C_1-C_6)alkyl]-SO_2-$; and $(C_1-C_6)alkoxy$ optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, $[(C_1-C_6)alkyl]-C(=O)-$, $(C_1-C_6)alkoxy$, $[(C_1-C_6)alkoxy]-C(=O)-$, $R^{a5}R^{a6}N-$ and $R^{a7}R^{a8}N-C(=O)-$, wherein R^{a5} , R^{a6} , R^{a7} and R^{a8} are independently selected from hydrogen, $(C_1-C_6)alkyl$, $[(C_1-C_6)alkyl]-$
 20 $C(=O)-$, $[(C_1-C_6)alkoxy]-C(=O)-$ and $[(C_1-C_6)alkyl]-SO_2-$; and
 Z is selected from $C(=O)$; $(CH_2)_{n8}$ wherein n8 is an integer selected from 0, 1 and 2;
 and

CHR^{Z1} wherein

25 R^{Z1} is selected from carboxy; $(C_1-C_6)alkoxy-C(=O)-$; non-, mono- and di-substituted amino wherein the substituents are independently selected from $(C_1-C_6)alkyl$, $[(C_1-C_6)alkyl]-C(=O)-$, $[(C_1-C_6)alkyl]-C(=O)-O-$ and $[(C_1-C_6)alkyl]-SO_2-$; $(C_1-C_6)alkyl$ optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, $[(C_1-C_6)alkyl]-C(=O)-$, $(C_1-C_6)alkoxy$, $[(C_1-C_6)alkoxy]-C(=O)-$, $R^{a1}R^{a2}N-$ and $R^{a3}R^{a4}N-C(=O)-$, wherein R^{a1} , R^{a2} , R^{a3} and R^{a4} are independently selected from hydrogen, $(C_1-C_6)alkyl$, $[(C_1-C_6)alkyl]-C(=O)-$, $[(C_1-C_6)alkoxy]-C(=O)-$ and $[(C_1-C_6)alkyl]-SO_2-$; and $[C(=O)-NR^{Z11}R^{Z12}]$ wherein R^{Z11} and R^{Z12} are independently selected from hydrogen and
 30

(C₁-C₆)alkyl optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, [(C₁-C₆)alkyl]-C(=O)-, (C₁-C₆)alkoxy, [(C₁-C₆)alkoxy]-C(=O)-, R^{a1}R^{a2}N- and R^{a3}R^{a4}N-C(=O)-, wherein R^{a1}, R^{a2}, R^{a3} and R^{a4} are independently selected from hydrogen, (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-.

Individual preferred compounds of this invention include 2,3-dihydro-1'-[3-oxo-3-(2,3,4,5-tetrahydro-1*H*-benzazepin-1-yl)propyl]spiro[1*H*-indene-1,4'-piperidine] or a salt thereof.

10

Another preferred class of compounds of this invention is that wherein

all R¹ are hydrogen

each R² is independently selected from hydrogen and halo;

X¹ and X² are independently selected from the group consisting of C[(C₁-C₆)alkyl] and C-OH;

15

W¹ and W² are both CH₂;

A is AB wherein

Y^b is selected from C(=O); CR^{Y1}R^{Y2}; CR^{Y3}[C(=O)R^{Y4}]; CR^{Y3}[NR^{Y5}C(=O)R^{Y4}]; CR^{Y3}[C(=O)NR^{Y6}R^{Y7}]; and CR^{Y3}[NR^{Y6}R^{Y7}];

20

Y^c is selected from O; S; SO₂; NH; N[(C₁-C₆)alkyl] wherein said (C₁-C₆)alkyl is optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, [(C₁-C₆)alkyl]-C(=O)-, (C₁-C₆)alkoxy, [(C₁-C₆)alkoxy]-C(=O)-, R^{a1}R^{a2}N- and R^{a3}R^{a4}N-C(=O)-, wherein R^{a1}, R^{a2}, R^{a3} and R^{a4} are independently selected from hydrogen, (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-; N-(CH₂)_{n3}-heterocyclyl wherein n₃ is an integer selected from 0, 1, 2 and 3, and said heterocyclyl contains from four to eight ring atoms one or two of which are independently selected from nitrogen, oxygen and sulfur; N-(CH₂)_{n4}-aryl wherein n₄ is an integer selected from 0, 1, 2 and 3, and said aryl is selected from phenyl and naphthyl; and N-(CH₂)_{n5}-heteroaryl wherein n₅ is an integer selected from 0, 1, 2 and 3, and said heteroaryl is a five to ten membered aromatic heterocyclyl containing from one to four hetero atoms independently selected from nitrogen, oxygen and sulfur; wherein

30

R^{Y1} and R^{Y2} are independently selected from hydrogen; hydroxy; non-, mono- and di-substituted amino wherein the substituents are independently selected from (C_1-C_6) alkyl; $[(C_1-C_6)alkyl]-C(=O)-$; $[(C_1-C_6)alkoxy]-C(=O)-$; $[(C_1-C_6)alkyl]-SO_2-$; and four- to eight-membered heterocyclyl containing one to four hetero atoms independently selected from nitrogen, oxygen and sulfur, wherein said heterocyclyl is optionally substituted with one to three substituents independently selected from hydroxy, (C_1-C_6) alkyl, $NH_2-C(=O)-$, $[(C_1-C_6)alkyl]-NH-C(=O)-$, $[(C_1-C_6)alkyl]_2-N-C(=O)-$, and non-, mono- and di-substituted amino wherein the substituents are independently selected from (C_1-C_6) alkyl, $[(C_1-C_6)alkyl]-C(=O)-$, $[(C_1-C_6)alkoxy]-C(=O)-$ and $[(C_1-C_6)alkyl]-SO_2-$; (C_1-C_6) alkyl optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, $[(C_1-C_6)alkyl]-C(=O)-$, $(C_1-C_6)alkoxy$, $[(C_1-C_6)alkoxy]-C(=O)-$, $R^{a1}R^{a2}N-$ and $R^{a3}R^{a4}N-C(=O)-$, wherein R^{a1} , R^{a2} , R^{a3} and R^{a4} are independently selected from hydrogen, (C_1-C_6) alkyl, $[(C_1-C_6)alkyl]-C(=O)-$, $[(C_1-C_6)alkoxy]-C(=O)-$ and $[(C_1-C_6)alkyl]-SO_2-$; and $(C_1-C_6)alkoxy$ optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, $[(C_1-C_6)alkyl]-C(=O)-$, $(C_1-C_6)alkoxy$, $[(C_1-C_6)alkoxy]-C(=O)-$, $R^{a5}R^{a6}N-$ and $R^{a7}R^{a8}N-C(=O)-$, wherein R^{a5} , R^{a6} , R^{a7} and R^{a8} are independently selected from hydrogen, (C_1-C_6) alkyl, $[(C_1-C_6)alkyl]-C(=O)-$, $[(C_1-C_6)alkoxy]-C(=O)-$ and $[(C_1-C_6)alkyl]-SO_2-$; or

R^{Y1} and R^{Y2} taken together with the carbon atom to which they are attached form spiropyrrolidinyl or spiropiperidinyl, both of which are optionally N-substituted with a substituent selected from (C_1-C_6) alkyl, $(C_1-C_6)alkyl-C(=O)-$, $[(C_1-C_6)alkyl]-C(=O)-(C_1-C_6)alkyl$ and aryl- $C(=O)-$ wherein aryl is selected from phenyl and naphthyl;

R^{Y3} is hydrogen;

R^{Y4} is selected from hydroxy; (C_1-C_6) alkyl optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, $[(C_1-C_6)alkyl]-C(=O)-$, $(C_1-C_6)alkoxy$, $[(C_1-C_6)alkoxy]-C(=O)-$, $R^{a1}R^{a2}N-$ and $R^{a3}R^{a4}N-C(=O)-$, wherein R^{a1} , R^{a2} , R^{a3} and R^{a4} are independently selected from hydrogen, (C_1-C_6) alkyl, $[(C_1-C_6)alkyl]-C(=O)-$, $[(C_1-C_6)alkoxy]-C(=O)-$ and

[(C₁-C₆)alkyl]-SO₂-; and (C₁-C₆)alkoxy optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, [(C₁-C₆)alkyl]-C(=O)-, (C₁-C₆)alkoxy, [(C₁-C₆)alkoxy]-C(=O)-, R^{a5}R^{a6}N- and R^{a7}R^{a8}N-C(=O)-, wherein R^{a5}, R^{a6}, R^{a7} and R^{a8} are independently selected from hydrogen, (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-; and

R^{Y5}, R^{Y6} and R^{Y7} are independently selected from hydrogen; (C₁-C₆)alkyl optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, [(C₁-C₆)alkyl]-C(=O)-, (C₁-C₆)alkoxy, [(C₁-C₆)alkoxy]-C(=O)-, R^{a1}R^{a2}N- and R^{a3}R^{a4}N-C(=O)-, wherein R^{a1}, R^{a2}, R^{a3} and R^{a4} are independently selected from hydrogen, (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-; heterocyclyl-(CH₂)_{n6}- wherein n₆ is an integer selected from 0, 1, 2, 3 and 4 and said heterocyclyl is four to eight membered containing one to three hetero atoms independently selected from nitrogen, oxygen and sulfur, wherein said heterocyclyl is optionally substituted with one to three substituents independently selected from hydroxy; (C₁-C₆)alkyl; NH₂-C(=O)-; (C₁-C₆)alkyl-NH-C(=O)-; [(C₁-C₆)alkyl]₂-N-C(=O)-; and non-, mono- and di-substituted amino wherein the substituents are independently selected from (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-; and heteroaryl-(CH₂)_{n7}- wherein n₇ is an integer selected from 0, 1, 2, 3 and 4 and said heteroaryl is five to ten membered containing one to three hetero atoms independently selected from nitrogen, oxygen and sulfur, wherein said heteroaryl is optionally substituted with one to three substituents independently selected from hydroxy; (C₁-C₆)alkyl; NH₂-C(=O)-; (C₁-C₆)alkyl-NH-C(=O)-; [(C₁-C₆)alkyl]₂-N-C(=O)-; and non-, mono- and di-substituted amino wherein the substituents are independently selected from (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-; or

R^{Y6} and R^{Y7} taken together with the nitrogen atom to which they are attached form a four to eight heterocyclyl optionally containing, in addition to the nitrogen atom, one to two additional hetero atoms independently selected from nitrogen, oxygen and sulfur, and said heterocyclyl is optionally

substituted with one substituent selected from hydroxy; (C₁-C₆)alkyl; NH₂-C(O=)-; (C₁-C₆)alkyl-NH-C(=O)-; [(C₁-C₆)alkyl]₂-N-C(=O)-; and non-, mono- and di-substituted amino wherein the substituents are independently selected from (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-;

said A is optionally substituted in the fused benzene rings with one to four substituents independently selected from halo; hydroxy; mercapto; phenyl; (C₁-C₆)alkyl optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, [(C₁-C₆)alkyl]-C(=O)-, (C₁-C₆)alkoxy, [(C₁-C₆)alkoxy]-C(=O)-, R^{a1}R^{a2}N- and R^{a3}R^{a4}N-C(=O)-, wherein R^{a1}, R^{a2}, R^{a3} and R^{a4} are independently selected from hydrogen, (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-; and (C₁-C₆)alkoxy optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, [(C₁-C₆)alkyl]-C(=O)-, (C₁-C₆)alkoxy, [(C₁-C₆)alkoxy]-C(=O)-, R^{a5}R^{a6}N- and R^{a7}R^{a8}N-C(=O)-, wherein R^{a5}, R^{a6}, R^{a7} and R^{a8} are independently selected from hydrogen, (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-; and Z is selected from C(=O); (CH₂)_{n8} wherein n8 is an integer selected from 0, 1 and 2; and

CHR^{Z1} wherein

R^{Z1} is selected from carboxy; (C₁-C₆)alkoxy-C(=O)-; non-, mono- and di-substituted amino wherein the substituents are independently selected from (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkyl]-C(=O)-O- and [(C₁-C₆)alkyl]-SO₂-; (C₁-C₆)alkyl optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, [(C₁-C₆)alkyl]-C(=O)-, (C₁-C₆)alkoxy, [(C₁-C₆)alkoxy]-C(=O)-, R^{a1}R^{a2}N- and R^{a3}R^{a4}N-C(=O)-, wherein R^{a1}, R^{a2}, R^{a3} and R^{a4} are independently selected from hydrogen, (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-; and [C(=O)-NR^{Z11}R^{Z12}] wherein R^{Z11} and R^{Z12} are independently selected from hydrogen and (C₁-C₆)alkyl optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, [(C₁-C₆)alkyl]-C(=O)-, (C₁-C₆)alkoxy, [(C₁-C₆)alkoxy]-C(=O)-, R^{a1}R^{a2}N- and R^{a3}R^{a4}N-C(=O)-, wherein R^{a1}, R^{a2}, R^{a3} and R^{a4} are independently selected from hydrogen, (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-

C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-.

Individual preferred compounds of this invention include 1'-[3-[(2*S*)-2-
[(dimethylamino)carbonyl]-2,3-dihydro-1*H*-indol-1-yl]-3-oxopropyl]spiro[(2-
5 hydroxy)indane-1,4'-piperidine] and 1'-[3-[(2*S*)-2-[(Dimethylamino)carbonyl]-2,3-
dihydro-1*H*-indol-1-yl]-3-oxopropyl]spiro[(3-methyl)indane-1,4'-piperidine] or a
salt thereof.

Accordingly, this invention relates to a pharmaceutical composition
10 comprising an effective amount of a compound of formula I defined as above and a
pharmaceutically acceptable carrier for treating a disease or medical condition
mediated by ORL1-receptor and its endogenous ligand in a mammal including a
human.

A preferred pharmaceutical composition of this invention comprises a
15 compound of formula I defined as above having selectivity for ORL-1 receptor.

A further preferred pharmaceutical composition of this invention comprises a
compound of formula I defined as above having antagonist effect for ORL-1 receptor.

A further preferred pharmaceutical composition of this invention comprises a
compound of formula I defined as above which is a selective antagonist for ORL-1
20 receptor.

Therefore, a pharmaceutical composition of this invention comprising a
compound of formula I defined as above is useful for treating or preventing a disease
or medical condition selected from pain; eating disorders including anorexia and
bulimia; anxiety and stress conditions; immune system diseases; locomotor disorder;
25 eating disorder; memory loss, cognitive disorders and dementia including senile
dementia and those diseases caused by Alzheimer's disease, Parkinson's disease or
other neurodegenerative pathologies; epilepsy or convulsion and symptoms associated
therewith; a central nervous system disorder related to glutamate release action, anti-
epileptic action, disruption of spatial memory, serotonin release, anxiolytic action,
30 mesolimbic dopaminergic transmission, rewarding properties of drug of abuse,
modulation of striatal and glutamate effects on locomotor activity; cardiovascular
disorders hypotension, bradycardia and stroke; renal disorders including water

excretion, sodium ion excretion and syndrome of inappropriate secretion of antidiuretic hormone (SIADH); gastrointestinal disorders; airway disorders including adult respiratory distress syndrome (ARDS); autonomic disorders including suppression of micturition reflex; metabolic disorders including obesity; cirrhosis with
5 ascites; sexual dysfunctions; and altered pulmonary function including obstructive pulmonary disease.

This invention also relates to a method for treating or preventing a disease or condition in a mammal including a human, which disease or condition is mediated by
10 ORL-1 receptor and its endogeneous ligand, comprising administering an effective amount of a compound of formula I defined as above to a mammal including a human, which suffered from such disease or condition.

More specifically, this invention relates to a method for treating or preventing the aforementioned disease or medical condition, wherein said compound has
15 selectivity for ORL-1 receptor.

More specifically, this invention relates to a method of treating or preventing the aforementioned disease or medical condition, wherein said compound has antagonist effect for ORL-1 receptor.

More specifically, this invention relates to a method for treating or preventing
20 the aforementioned disease or medical condition, wherein said compound is a selective antagonist for ORL-1 receptor.

Accordingly, this invention relates to a method for treating or preventing the aforementioned disease or medical condition wherein said disease or condition is selected from pain; eating disorders including anorexia and bulimia; anxiety and stress
25 conditions; immune system diseases; locomotor disorder; eating disorder; memory loss, cognitive disorders and dementia including senile dementia and those diseases caused by Alzheimer's disease, Parkinson's disease or other neurodegenerative pathologies; epilepsy or convulsion and symptoms associated therewith; a central nervous system disorder related to glutamate release action, anti-epileptic action, disruption of spatial
30 memory, serotonin release, anxiolytic action, mesolimbic dopaminergic transmission, rewarding properties of drug of abuse, modulation of striatal and glutamate effects on locomotor activity; cardiovascular disorders hypotension, bradycardia and stroke; renal

disorders including water excretion, sodium ion excretion and syndrome of inappropriate secretion of antidiuretic hormone (SIADH); gastrointestinal disorders; airway disorders including adult respiratory distress syndrome (ARDS); autonomic disorders including suppression of micturition reflex; metabolic disorders including obesity; cirrhosis with ascites; sexual dysfunctions; and altered pulmonary function including obstructive pulmonary disease.

General Synthesis:

The compounds of formula I of the present invention may be prepared according to known preparation methods, or General Procedures or preparation methods illustrated in the following reaction Schemes. Unless otherwise indicated R¹, R², X¹, X², W¹, W², A and Z, and groups or substituents thereof, in the reaction Schemes and discussion that follow are defined as above. Unless otherwise indicated, reactions in this specification may be carried out at about ambient pressure (i.e., 760 mmHg) and about room temperature (i.e., 25°C).

Typical preparation procedures for compounds of formula I of the present invention are as follow:

Protecting Groups:

Amino, hydroxy, mercapto or the like may be protected with a protecting group, and the protectinng group may be subsequently removed in an appropriate reaction step according to a known procedure (e.g., Protective Groups in Organic Synthesis edited by T. W. Greene *et al.* (John Wiley & Sons, 1991)). For example, a primary or a secondary amine may be typically protected by reaction with benzyl chloride in K₂CO₃ solution, and the benzyl group (abbreviated as Bn) may be removed by catalytic hydrogenation over palladium-carbon. Introduction for *t*-butoxycarbonyl (abbreviated as Boc) to amino group may be carried out using (BOC)₂O under basic condition, and the protecting group may be removed in HCl/EtOAc. Hydroxy may be protected with *t*-butyldimethylsilyl (abbreviated as TBS or TBDMS) in alkylation using NaH. The protecting group may be introduced with TBDMSCl in imidazole and DMF and removed using an appropriate reagent such as tetrabutylammonium

fluoride.

Leaving Groups / Introductions of Sulfonyl Groups:

Leaving group used in a reaction described hereafter are known to those skilled in the art. These leaving groups include halo such as Cl, Br and I; sulfonic esters such as TfO (triflates), MsO (mesylates), TsO (tosylates); and the like. These groups may be introduced to an appropriate compound according to methods known to those skilled in the art (e.g., (a) halogenation using triphenylphosphine/CX₄ wherein X is halo (PPh₃/CX₄); (b) reaction with TsCl; and (c) reaction with MsCl).

Halogenations:

Halogenations may be used for displacement of hydroxy group by a halogen atom. These halogenations are typically carried out using halogenating reagents such as hydrogen halogenide (e.g., HCl, HBr or HI), sulfinyl halogenide (e.g., SOCl₂ or SOBr₂), phosphorous halides (PCl₃, PCl₅, PBr₃ or PBr₅), phosphoryl chloride (POCl₃), Ph₃PCl₂, Ph₃P-CCl₄ system, a combination of *N*-bromosuccinimide (NBS) or 1,3-dibromo-5,5-dimethylhydantoin with Ph₃P in DMF, Ph₃PBr₂, system of Ph₃P-diethyl azodicarboxylate-hydroxy compound-LiBr, trimethylsilyl bromide (Me₃SiBr) or trimethylsilyl chloride (Me₃SiCl) and LiBr, white or red phosphorous and I₂, diphosphorous tetraiodide (P₂I₄), trimethylsilyl iodide (Me₃SiI) and sodium iodide (NaI), trimethylsilyl polyphosphate (PPSE), a fluorobenzothiazolium or fluoropyridinium salt, carbodiimidinium iodide or the like. If appropriate, these halogenations may be carried out in a reaction inert solvent such as DMF, hexamethylphosphoric triamide (HMPA), or the like. These halogenations may be typically carried out at a temperature from about 0°C to about the reflux temperature of the reaction mixture from about 1 minutes to about 10 hours.

Alkylations:

Alkylations may be carried out according to a procedure known to those skilled in the art. More specifically, a primary or secondary amine may be alkylated to a secondary or tertiary amine with a halo alkyl in the presence of an alkali metal ion such as potassium ion, base or a mixture thereof. This alkylation may be also carried out

using a nucleophilic strong base that serves to remove the proton of the secondary amine radical. Instead of halides, sulfates or sulfonates may be used in these reactions. Alkylations of alcohols may be carried out using diazo compounds preferably in the presence of a catalyst such as fluoboric acid (HBF_4) or silica gel.

- 5 For the alkylations, suitable solvents include polar aprotic solvents such as dimethylformamide (DMF), dimethylsulfoxide, acetonitrile (MeCN), acetone, sulfur dioxide, dichloromethane, hexane and the like; and protic solvents such as water, alcohols such as methanol (MeOH) and ethanol (EtOH), ethylene glycol and the like, or a combination thereof. These reactions may be typically carried out at a
- 10 temperature from about 0°C to the reflux temperature of a solvent to be used for from about 1 minute to 30 hours.

Michael Reaction may be carried out in the presence of a base. Suitable bases for this reaction include NaOC_2H_5 , KOH, $\text{KOC}(\text{CH}_3)_3$, triethylamine (Et_3N), NaH, BuLi, lithium diisopropylamide (LDA) and the like.

- 15 Alkylation of cyclic amines may be carried out using metal hydride reagents. Suitable hydride reagents for this reaction include borohydrides such as NaBH_4 , $\text{NaBH}(\text{OAc})_3$ and NaBH_3CN . This reaction may be preferably carried out under mildly acidic conditions. For example, alkylation of a cyclic amine with an aldehyde or ketone compound may be typically carried out using $\text{NaBH}(\text{OAc})_3$ or NaBH_3CN
- 20 and an acid such as acetic acid or HCl in a reaction inert solvent such as CH_2Cl_2 , an alcohol (e.g., MeOH, EtOH or *i*-PrOH), THF, MeCN or the like.

Aminations:

- Aminations of alkanols or alkyl halides may be carried out by reactions with cyclic
- 25 imide compounds such as N-phthalimides followed by hydrazinolysis or hydrolysis. If required, the reactions with phthalimides may be carried out using organophosphorous reagents with or without azo compounds.

Amidations:

- 30 Amidation 1 – Dehydration of Ammonium Salts:

Amidations of carboxylic acids and amines may be carried out at elevated temperatures. This reaction may be catalyzed by acid or by cation exchange resin.

Amidation 2 - Acylation of Amines by Acyl Halides:

Acyl halides may be treated with ammonia or amines for the preparation of amides. This reaction is usually carried out in the presence of a base such as triethylamine or potassium carbonate to take up the evolving hydrogen halide. If appropriate, a coupling agent such as carbodiimide may be used. The reaction temperature may be controlled by cooling or dilution. Acyl halide may also be reacted with arylamines, hydrazine or hydroxylamine under the similar conditions. Amino protections using carbobenzoxy group (abbreviated as Cbz) or t-butoxycarbonyl group (abbreviated as Boc) may be carried out in this way.

Amidation 3 - Acylation of Amines by Carboxylic Acid Anhydrides:

This reaction may be carried out with ammonia or primary or secondary amines according to a similar procedure for acylation of amines by acyl halides.

Amidation 4 - Acylation of Amines by Carboxylic acids:

Carboxylic acids may be treated with ammonia or amine compounds to give amides. This amidation may be carried out in the presence of a coupling agent with or without an additional base at about room temperature. Suitable coupling agents include carbodiimides such as dicyclohexylcarbodiimide (DCC) used in a peptide synthesis. Other suitable coupling agents used in these amidations include N,N'-carbonyldiimidazole (CDI), diisopropylcarbodiimide (DIPC), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (WSC, water soluble carbodiimide), benzotriazole-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate (BOP), diphenylphosphorylazide (DPPA) and the like. A cyclic amine may be acylated according to a method analogous to these amidations. If amines are subjected to this reaction in its halogen salt forms, additional amines may be used for trapping hydrogen halides formed.

Amidation 5 - Acylation of Amines by Carboxylic Esters:

Carboxylic esters may be converted to unsubstituted, N-substituted or N,N-disubstituted amides. This reaction may be carried out in the presence of a strong

base catalysis as well as catalysis by cyanide ion under a high pressure. Hydrazides and hydroxamic acids may be prepared from carboxylic esters with hydrazine and hydroxylamine respectively under similar reaction conditions.

5 Amidation 6 – Acylation of Amines by Amides or Other Acid Derivatives:

A salt of an amine may be subjected to this reaction. In this reaction, NH_2 usually acts as a leaving group. Secondary and primary amines (in the form of their salts) are the most common reagents in this reaction. Acid derivatives, which may be converted to amides, include thiol acids, thiol ethers, acyloxyboranes, 1,1,1-trihalo
10 ketones, α -keto nitrils, acyl azides and the like.

These amidations may be carried out in a reaction inert solvent such as dichloromethane (CH_2Cl_2), alcohols such as methanol, ethanol or butanol (BtOH), acetonitrile, tetrahydrofuran (THF), dimethylfuran (DMF), or pyridine or a combination
15 thereof, at a temperature from about 0°C to the reflux temperature of a solvent, for from about 5 minutes to 48 hours.

Hydrolysis of Esters:

Hydrolysis of esters may be carried out in the presence of an acid, base, metal ion, enzyme or nucleophile according to a method known to those skilled in the art. The
20 hydrolysis of esters may be carried out in a reaction inert solvent at a temperature from about 0°C to the reflux temperature of the solvent for from about 1 to 24 hours. Suitable solvents for the reactions include alcohols such as methanol, ethanol, tetrahydrofuran, acetic acid and the like.

25

Esterifications:

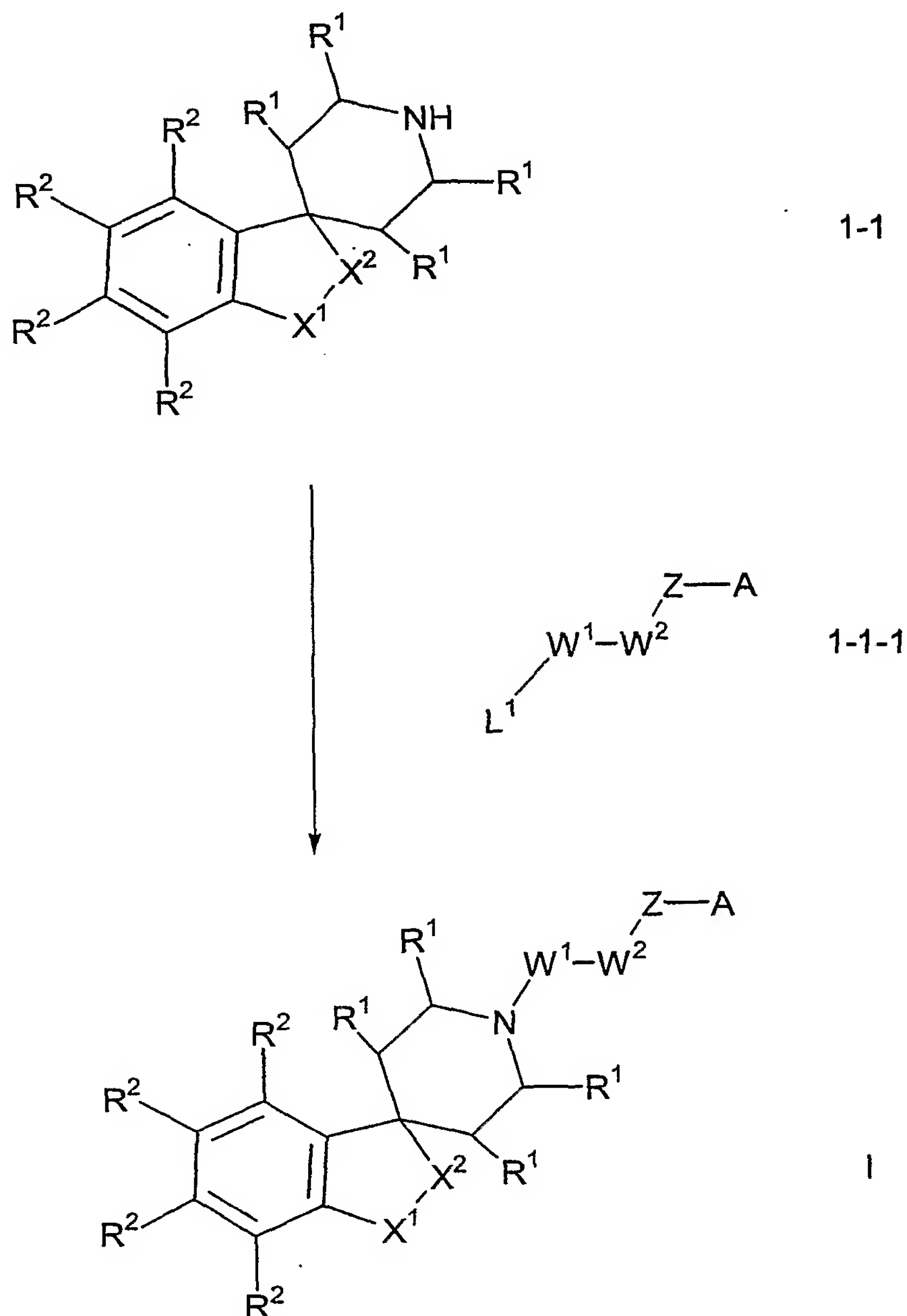
Carboxylic acids and alcohols afford esters using acid catalysis. Typical catalysis for this reaction include conc. HCl, anhydrous sulfuric acid, *p*-toluenesulfonic acid and the like. The alcohol generally serves as the solvent, but other reaction inert solvent
30 such as toluene or xylene may be used. The alcohol may be used in large excess, and the water from the reaction mixture may be removed.

Reductions:

Reductions may be carried out using reducing agents such as hydride reagents. Typical reducing reagents are lithium aluminum hydride (LiAlH_4), lithium triethylborohydride (LiEt_3BH), lithium trialkoxyaluminum hydride (e.g., $\text{LiAlH}(\text{OMe})_3$ and $\text{LiAlH}(\text{OBu-tert})_3$), $\text{LiAlH}_4\text{-AlCl}_3$, diisobutylaluminum hydride (DIBAL-H), NaBH_4 , $\text{NaBH}(\text{OAc})_3$, $\text{Me}_4\text{NBH}(\text{OAc})_3$, NaBH_3CN , LiBH_4 , LiR_3BH , $[(\text{C}_2\text{H}_5)_3\text{SiH}]$, B_2H_6 , dialkylboron (R_2BH) or the like. Other reducing agents are zinc with acid or base, SnCl_2 , chromium(II) ion and the like. This reaction may be carried out in an inert solvent at a temperature from about -78°C to about the reflux temperature of the solvent. For example, reduction using LiAlH_4 may be carried out in tetrahydrofuran, and reduction using NaBH_4 may be carried out in an alcohol such as methanol (MeOH) or ethanol (EtOH).

Schemes 1-1, 1-2 and 1-3 illustrate embodiments of preparation process for a compound of formula (I).

SCHEME 1-1



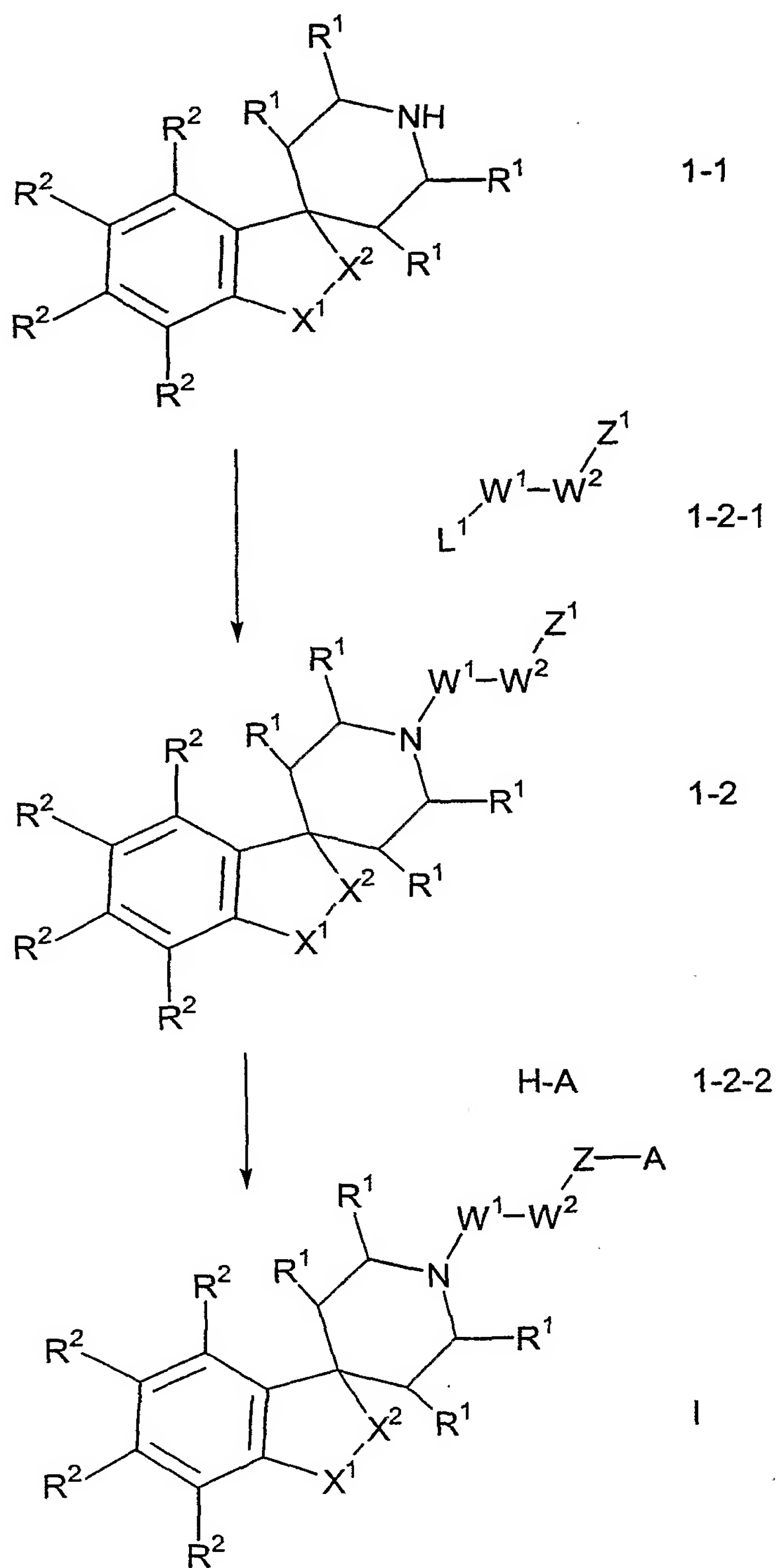
Scheme 1-1 illustrates a preparation method of a compound of formula I of the present invention. This method comprises alkylation of a spiro-piperidine compound of formula 1-1 by a compound of formula 1-1-1 wherein L^1 is a leaving group. This reaction may be carried out according to an alkylation of an amine compound. In a preferred embodiment of this reaction, a compound of formula 1-1

may be used as potassium salt, then reacted with a compound of formula 1-1-1 wherein the leaving group L^1 may be halo. The potassium salt of a compound formula 1-1 may be prepared by treating said compound with a potassium salt such as potassium carbonate, potassium hydroxide or a combination thereof. The following

5 alkylation may be carried out at an elevated temperature, for example at about the reflux temperature of a reaction inert solvent used. Typically, this reaction may be carried out in acetonitrile (MeCN) using potassium carbonate (K_2CO_3) and potassium iodide (KI).

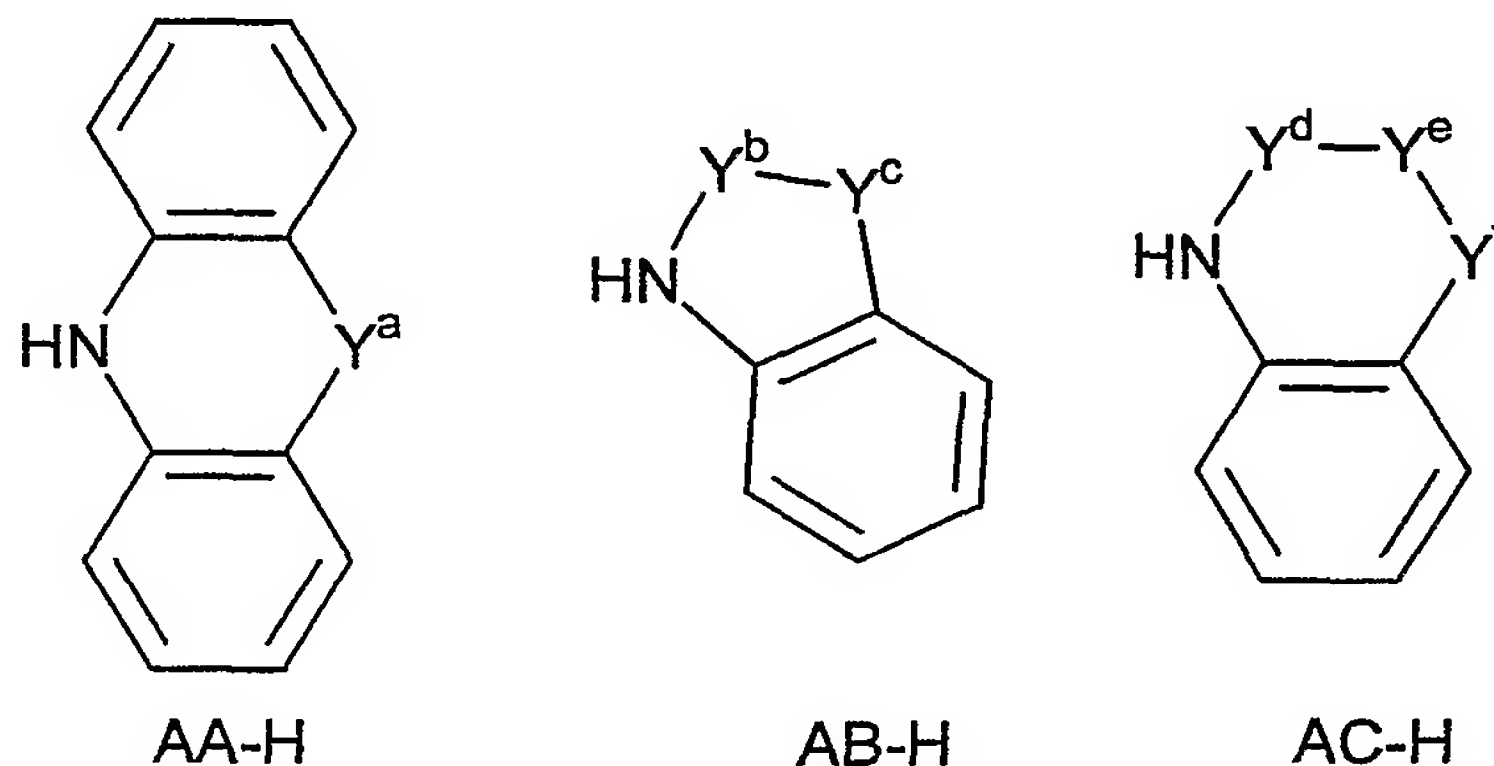
10 Scheme 1-2 illustrates another preparation method of a compound of formula (I).

SCHEME 1-2



A compound of formula I may be prepared from a compound of formula 1-1

by alkylation with a compound of formula 1-2-1 followed by an amination with a compound of formula 1-2-2. In formula 1-2-1, Z^1 is Z as defined in formula (I) or its analogous group comprising a leaving group, carbonyl, hydroxy or carboxy; and L^1 is a leaving group similar to L^1 in formula 1-1-1 described in Scheme 1-1. Formula 1-2-2 means either of formulae AA-H, AB-H and AC-H as described below.



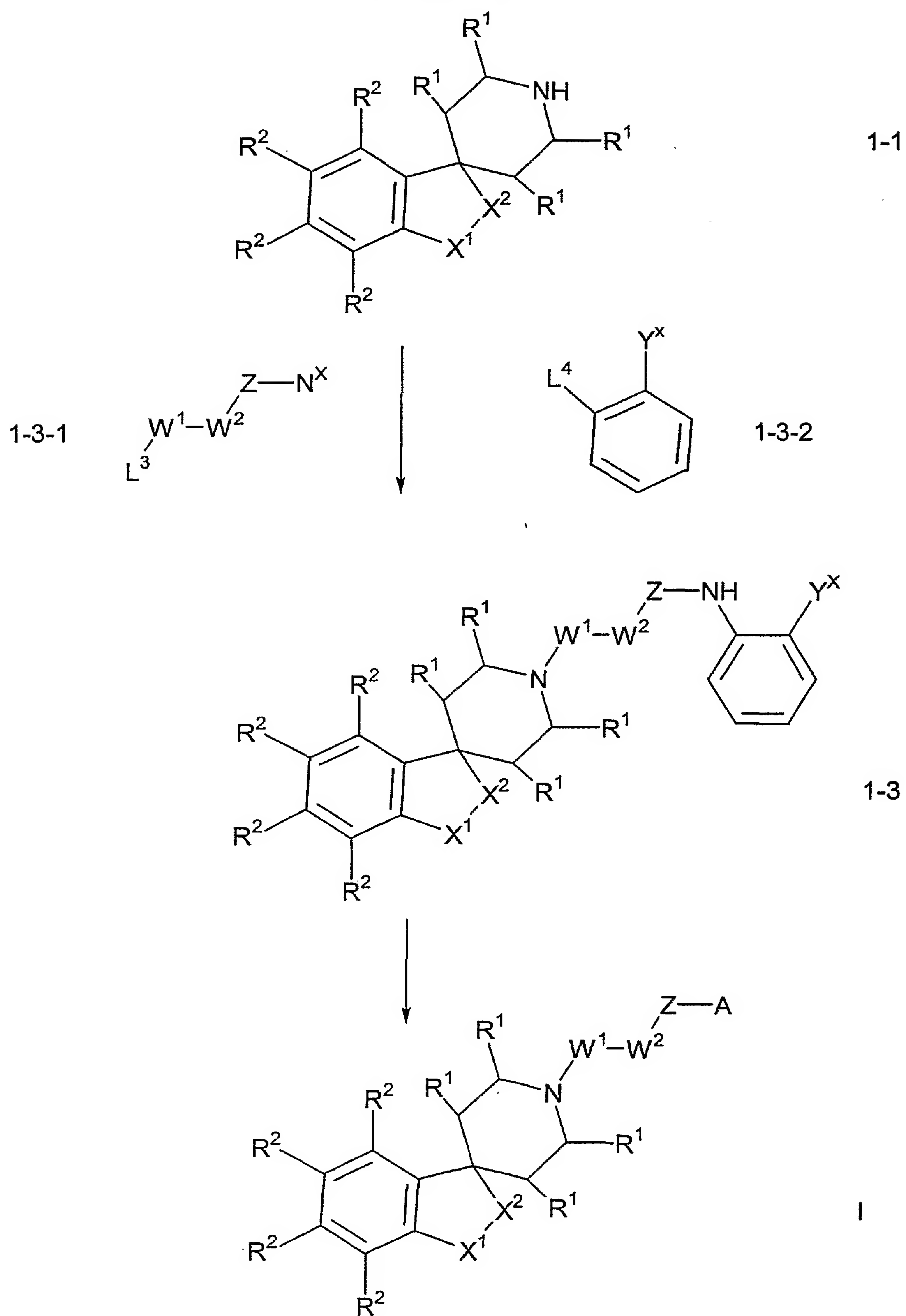
Namely, these compounds are reduced forms of substituent represented by "A" in formula (I) in this specification.

Alkylation of a compound of formula 1-1 with a compound of formula 1-2-1 may be carried out under similar conditions described in Scheme 1-1 in this specification to afford a compound of formula 1-2.

Then, the compound of formula 1-2 thus obtained may be reacted with a compound of formula 1-2-2. A compound of formula 1-2 wherein Z^1 comprises a leaving group may be coupled with a compound of formula 1-2-2 by alkylation under similar reaction conditions as described in Scheme 1-1 or 1-2 in this specification. A compound of formula 1-2 wherein Z^1 comprises carboxy may be coupled with a compound of formula 1-2-2 by amidation by a peptide formation known to those skilled in the art.

A compound of formula I of the present application wherein A is AB as defined above may be also prepared according to a preparation method described in Scheme 1-3.

SCHEME 1-3



Preparation processes in Scheme 1-3 is preferably useful for compounds of formula I wherein in A is an optionally substituted benzofused heteroaryl ring containing a nitrogen atom and additional hetero atoms. A typical benzofused ring in the compounds is benzimidazolyl, benzothiazolyl or benzoxazolyl ring.

5 As shown in Scheme 1-3 the preparation process comprises:

Step 1 – reaction between compounds of formula 1-1 may be reacted with compounds of formula 1-3-1, wherein L^3 is a leaving group such as halo and N^x is amino, phthalimido or the like;

10 Step 2 – reaction between compounds obtained in Step 1 with compounds of formula 1-3-2 to give compounds of formula 1-3; and

Step 3 – cyclization of compounds of formula 1-3 to yield compounds of formula 1.

The reactions in Step 1 and 2 are alkylations of amine compounds. These reactions may be typically carried out in the presence of potassium ion. Resulting
15 compounds in Step 1 wherein N^x is phthalimido may be converted to amine by deprotection with hydrazine prior to Step 2. The reaction in Step 3 may be carried out using carboxylic acids optionally in the presence of acid or a cyano halide.

The subject invention also includes isotopically-labelled compounds, which
20 are identical to those recited in formula (I), but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, fluorine and chlorine, such as 2H , 3H , ^{13}C , ^{14}C , ^{15}N , ^{18}O ,
25 ^{17}O , ^{31}P , ^{32}P , ^{35}S , ^{18}F , and ^{36}Cl , respectively. Compounds of the present invention, prodrugs thereof, and pharmaceutically acceptable salts of said compounds or of said prodrugs which contain the aforementioned isotopes and/or other isotopes of other atoms are within the scope of this invention. Certain isotopically-labelled compounds of the present invention, for example those into which radioactive isotopes such as 3H and ^{14}C are incorporated, are useful in drug and/or substrate tissue distribution assay.
30 Tritiated, i.e., 3H , and carbon-14, i.e., ^{14}C , isotopes are particularly preferred for their ease of presentation and detectability. Further, substitution with heavier isotopes

such as deuterium, i.e., ^2H , can afford therapeutic advantage resulting from greater metabolic stability, for example increased *in vivo* half-life or reduced dosage requirement and, hence, may be preferred in some circumstances. Isotopically labelled compounds of formula (I) of this invention and prodrugs thereof can generally
5 be prepared by carrying out the procedure disclosed in above-disclosed Schemes and/or Examples and Preparations below, by submitting a readily available isotopically labelled reagent for a non-isotopically labelled reagent.

The compounds of Formula (I) of this invention are basic, therefore they will
10 form acid-addition salts. All such salts are within the scope of this invention. However, it is necessary to use an acid addition salt which is pharmaceutically-acceptable for administration to a mammal. The acid-addition salts can be prepared by standard methods. For example, the salts may be prepared by contacting the basic compounds with acid in substantially equivalent proportions in water or an organic
15 solvent such as methanol or ethanol, or a mixture thereof. The salts can be isolated by crystallization from or evaporation of the solvent. Typical salts which can be formed are the hydrochloride, nitrate, sulfate, bisulfate, phosphate, acetate, lactate, citrate, tartrate, succinate, maleate, fumarate, gluconate, saccharate, benzoate, methanesulfonate, ethanesulfonate, benzenesulfonate, p-toluenesulfonate, oxalate and
20 pamoate (1,1'-methylene-bis-(2-hydroxy-3-naphthoate)) salts.

In addition, when the compounds of this invention form hydrates or solvates they are also within the scope of this invention.

25 The compounds of Formula (I) have been found to possess selective affinity for ORL1-receptors and ORL-1 receptor antagonist activity. Thus, these compounds are useful as an analgesic, anti-inflammatory, diuretic, anesthetic, neuroprotective, anti-hypertensive and anti-anxiety agent, and the like, in mammalian subjects, especially humans in need of such agents. The affinity, antagonist activities and
30 analgesic activity can be demonstrated by the following tests respectively.

Selective Affinity for ORL1-receptors:

ORL1-Receptor Binding Assay:

The human ORL1 receptor transfected HEK-293 cell membranes were incubated for 45 min at 22°C with 0.4 nM [³H]nociceptin, 1.0 mg of wheat germ agglutinin-coated SPA beads and various concentrations of test compounds in a final volume of 200 μ l of 50 mM HEPES buffer pH7.4 containing 10 mM MgCl₂ and 1 mM EDTA. Non-specific binding was determined by the addition of 1 μ M unlabeled nociceptin. After the reaction, the assay plate was centrifuged at 1,000 rpm for 1 min and then the radioactivity was measured by a Liquid Scintillation Counter.

 μ -Receptor Binding Assay:

The human Mu receptor transfected CHO-K1 cell membranes were incubated for 45 min at 22°C with 1.0 nM [³H]DAMGO, 1.0 mg of wheat germ agglutinin-coated SPA beads and various concentrations of test compounds in a final volume of 200 μ l of 50 mM Tris-HCl buffer pH7.4 containing 5 mM MgCl₂. Non-specific binding was determined by the addition of 1 μ M unlabeled DAMGO. After the reaction, the assay plate was centrifuged at 1,000 rpm for 1 min and then the radioactivity was measured by a Liquid Scintillation Counter.

Each percent non specific binding thus obtained is graphed as a function of compound concentration. A sigmoidal curve is used to determine 50% bindings (i.e., IC₅₀ values).

In this testing, the preferred compounds prepared in the working examples appearing hereafter demonstrated higher binding affinity for ORL1-receptors than for mu-receptors.

$$IC_{50} \text{ (ORL1-receptors) nM} / IC_{50} \text{ (mu-receptors) nM} < 1.0$$

ORL1 Receptor Functional assay:

The human ORL1 receptor transfected HEK-293 cell membranes were incubated with 400pM [³⁵S]GTP γ S, 50 nM nociceptin and various concentrations of test compounds in

assay buffer (20 mM HEPES, 100 mM NaCl, 5 mM MgCl₂, 1 mM EDTA, 5 mM GDP, 1 mM DTT, pH7.4) containing 1.5mg of wheat germ agglutinin-coated SPA beads for 60 or 90 min at 25°C in a final volume of 200 µl. Basal binding was assessed in the absence of nociceptin and non-specific binding was defined by the addition of
5 unlabelled 10 mM GTPγS. Membrane-bound radioactivity was detected by a Liquid Scintillation Counter.

Analgesic Tests:

Tail Flick Test in Mice:

10 The latency time to withdrawal of the tail from radiant heat stimulation is recorded before and after administration of test compounds. Cut-off time is set to 8 sec.

Acetic Acid Writhing Test in Mice:

Acetic acid saline solution of 0.7 % (v/v) is injected intraperitoneally (0.16 ml/10 g
15 body weight) to mice. Test compounds are administered before acetic acid injection. As soon as acetic acid injection, animals are placed in a 1 liter beaker and writhing is recorded for 15 min.

Formalin Licking Test in Mice:

20 Formalin-induced hind paw licking is initiated by a 20 micro liters subcutaneous injection of a 2 % formaline solution into a hind paw of mice. Test compounds are administered prior to formalin injection. Total licking time is recorded for 45 min after formalin injection.

Carrageenan-Induced Mechanical Hyperalgesia Test in Rats:

The response to mechanical nociceptive stimulus is measured using an algometer (Ugo Basile, Italy). The pressure is loaded to the paw until rats withdrawal the hind paw. Lambda-Carrageenan saline solution of 1 % (w/v) is injected subcutaneously into the hind paw and the withdrawal response is measured before and after the
30 injection. Test compounds are administered at appropriate time point.

Carrageenan-Induced Thermal Hyperalgesia Test in Rats:

The response to thermal nociceptive stimulus is measured using an plantar test apparatus (Ugo Basile, Italy). The radiant heat stimuli is applied to the paw until rats withdrawal the hind paw. Lambda-Carrageenan saline solution of 2 % (w/v) is injected subcutaneously into the hind paw and the withdrawal response is measured before and after the injection. This testing method is described in K. Hargreaves, et al., Pain 32:77-88, 1988.

Chronic Constriction Injury Model (CCI Model):

Chronic constriction injury is made according to Bennett's method (Bennett, et al., Pain 83:169-182, 1999). Tactile allodynia in rats is assessed using the von Frey hairs (Stoelting, IL) before and after administration with test compounds.

The compounds of Formula (I) of this invention can be administered by conventional pharmaceutical practice via either the oral, parenteral or topical routes to mammals, for the treatment of the indicated diseases. For administration to human patient by either route, the dosage is in the range of about 0.01mg/kg to about 3000mg/kg body weight of the patient per day, preferably about 0.01mg/kg to about 1000mg/kg body weight per day administered singly or as a divided dose. However, variations will necessarily occur depending upon the weight and condition of the subject being treated, compound employed, the disease state being treated and the particular route of administration chosen.

The compounds of the present invention may be administered alone or in combination with pharmaceutically acceptable carriers by either of the above routes previously indicated, and such administration can be carried out in single or multiple doses. Generally, the compounds can be combined with various pharmaceutically acceptable carriers in the form of tablets, powders, capsules, lozenges, trochees, hard candies, powders, sprays, creams, salves, suppositories, jellies, gels, pastes, lotions, ointments, suspensions, solutions, elixirs, syrups or the like. Such pharmaceutical carriers include solvents, excipients, coating agents, bases, binders, lubricants, disintegrants, solubilizing agents, suspending agents, emulsifying agents, stabilizers, buffering agents, tonicity agents, preservatives, flavoring agents, aromatics, coloring

agents and the like.

For example, the tablets can contain various excipients such as starch, lactose, glucose, microcrystalline cellulose, calcium sulfate, calcium carbonate, talc, titanium oxide and the like, coating agents such as gelatin, hydroxypropylcellulose and the like, binding agents such as gelatin, gum arabic, methylcellulose and the like, and the disintegrating agents such as starch, agar, gelatine, sodium hydrogencarbonate and the like. Additionally, lubricating agents such as magnesium stearate and talc are often very useful for tableting purposes. Solid compositions of a similar type may also be employed as fillers in gelatine capsules; preferred materials in this connection also include lactose as well as high molecular weight polyethylene glycols. When aqueous suspensions and/or elixirs are desired for oral administration, the active ingredient may be combined with various sweetening or flavoring agents, coloring matter or dyes, and, if so desired, emulsifying and/or suspending agents as well, together with diluents such as water, ethanol, propylene glycol, glycerin and various like combinations thereof.

In general, the therapeutically-effective compounds of this invention are present in such oral dosage forms at concentration levels ranging 5% to 70% by weight, preferably 10% to 50% by weight.

The compounds of the present invention in the form of a solution may be injected parenterlly such as intradermaly, subcutaneously, intravenously or intramuscularly. For example the solutions are sterile aqueous solutions, aqueous suspensions and an edible oil solutions. The aqueous solutions may be suitably buffered (preferably pH>8), and may contain enough salts or glucose to make the solution isotonic with blood. The aqueous solutions are suitable for intravenous injection purposes. The aqueous suspensions may contain a suitable dispersing or suspending agents such as sodium carboxymethylcellulose, methylcellulose, polyvinylpyrrolidone or gelatin. The aqueous suspensions can be used for subcutaneous or intramuscular injections. The edible oil such as cottonseed oil, sesame oil, coconut oil or peanut oil can be employed for the edible oil solutions. The oil solutions are suitable for intra-articular, intra-muscular and subcutaneous injection. The preparation of all these solutions under sterile conditions is readily accomplished by standard pharmaceutical techniques well-known to those skilled in

the art.

It is also possible to administer the compounds of the present invention topically when treating inflammatory conditions of the skin and this may preferably be done by way of creams, jellies, gels, pastes, ointments and the like, in accordance with standard pharmaceutical practice.

Examples and Preparations

The present invention is illustrated by the following examples and preparation. However, it should be understood that the invention is not limited to the specific details of these examples and preparations. Melting points were taken with a Buchi micro melting point apparatus and is not corrected. Infrared Ray absorption spectra (IR) were measured by a Shimadzu infrared spectrometer (IR-470). ^1H and ^{13}C nuclear magnetic resonance spectra (NMR) were measured in CDCl_3 by a JEOL NMR spectrometer (JNM-GX270, 270MHz) unless otherwise indicated and peak positions are expressed in parts per million (ppm) downfield from tetramethylsilane. The peak shapes are denoted as follows: s, singlet; d, doublet; t, triplet; m, multiplet; br, broad.

Analytical data of compounds, which can be prepared according to General Procedures A and B or were prepared in Examples hereinafter disclosed, can be taken by utilizing Waters LC-MS system (LC as 2690, ZMD as MS).

Analytical condition for LC-MS: Column YMC CombiScreen basic 4.6 mm x 50 mm, Flow rate 1 mL/min.; Mobile phase 20% MeOH/ 80% 0.1% HCO_2H in H_2O programmed over 5min to 90% MeOH/10% 0.1% HCO_2H in H_2O . Hold for 5 min.; Wave length 220-400 nm. MS detector ApcI Cone 30 Volts.

Preparation 1

2,3-Dihydro-1'-[2-(ethoxycarbonyl)ethyl]spiro[1*H*-indene-1,4'-piperidine]

A mixture of 2,3-dihydrospiro[1*H*-indene-1,4'-piperidine] hydrochloride (1.00 g, 4.47 mmol, this was prepared according to known procedure : M. S. Chambers *et al*, *J. Med. Chem.* **1992**, 35, 2033), ethyl 3-bromopropionate (1.62 g, 8.94 mmol) and *N,N*-diisopropylethylamine (1.73 g, 13.4 mmol) in EtOH (20 ml) was stirred at 65 °C for 18 h. Then the reaction mixture was concentrated, basified with NaHCO_3 solution, and extracted with CH_2Cl_2 . The extracts combined were dried (MgSO_4), filtered, and

concentrated. The residue was purified by silica gel column chromatography (CH₂Cl₂/MeOH: 40/1 as eluent) to give 1.28 g (99 %) of title compound as colorless oil.

¹H NMR (300 MHz, CDCl₃) δ 7.22-7.12 (4H, m), 4.46 (2H, q, J=7.2Hz), 2.95-2.83(6H, m), 2.80-2.73 (2H, m), 2.60-2.52(2H, m), 2.28-2.18 (2H, m), 2.03-1.87 (4H, m), 1.60-1.50 (2H, m), 1.28 (3H, t, J=7.2Hz).

MS(EI direct) m/z : 287(M)⁺.

Preparation 2

2,3-Dihydro-1'-[2-(carboxy)ethyl]spiro[1*H*-indene-1,4'-piperidine] hydrochloride

A mixture of 2,3-dihydro-1'-[2-(ethoxycarbonyl)ethyl]spiro[1*H*-indene-1,4'-piperidine] (1.28 g, 4.45 mmol), 2N HCl (10 ml) and AcOH (10 ml) was stirred at 100 °C for 20 h. After cooling down to 0 °C, the resulting white solid appeared was collected by filtration, washed with AcOEt, and dried to afford 1.13 g (86 %) of title compound as a white solid.

¹H NMR (300 MHz, DMSO-*d*₆) δ 10.20 (1H, br.s), 7.25-7.10 (4H, m), 3.50-3.00 (6H, m), 2.89-2.82 (4H, m), 2.23-2.08 (2H, m), 2.04 (2H, t, J=7.2Hz), 1.70-1.60 (2H, m).

MS(ESI positive) m/z : 260(M+H)⁺.

Preparation 3

2,3-Dihydro-1'-[2-(chloroformyl)ethyl]spiro[1*H*-indene-1,4'-piperidine]

hydrochloride

To a stirred suspension of 2,3-dihydro-1'-[2-(carboxy)ethyl]spiro[1*H*-indene-1,4'-piperidine] hydrochloride (0.80 g, 2.70 mmol) in thionyl chloride (6 ml) was added DMF (0.2 ml) at room temperature. After 1 h stirring, the reaction mixture was diluted with mixed solvents (CH₂Cl₂/hexane: 1/1). The resulting solid appeared was collected by filtration and dried to give 0.77 g (91 %) of title compound as white solid.

¹H NMR (300 MHz, DMSO-*d*₆) δ 10.81 (1H, br.s), 7.25-7.09 (4H, m), 3.52-3.42 (2H, m), 3.36-3.27 (2H, m), 3.17-3.01 (2H, m), 2.94-2.86 (4H, m), 2.31-2.18 (2H, m), 2.06 (2H, t, J=7.2 Hz), 1.69-1.59 (2H, m).

MS(EI direct) m/z : 277(M)⁺.

Example 1

2,3-Dihydro-1'-[3-(2-methoxycarbonylindolin-1-yl)-3-oxopropyl]spiro[1*H*-indene-1,4'-piperidine] hydrochloride

To a stirred solution of methyl indoline-2-carboxylate (152 mg, 0.86 mmol) and triethylamine (0.36 ml, 2.58 mmol) in CH₂Cl₂ (5 ml) was added 2,3-dihydro-1'-[2-(chloroformyl)ethyl]spiro[1*H*-indene-1,4'-piperidine] hydrochloride (270 mg, 0.86 mmol) at room temperature and the resulting reaction mixture was stirred for 5 h. The reaction mixture was poured into a saturated aqueous NaHCO₃ solution and extracted with CH₂Cl₂. The extracts combined were washed with brine, dried (MgSO₄), filtered, and concentrated. The residue was purified by silica gel column chromatography (CH₂Cl₂/MeOH: 30/1 as an eluent) to give 160 mg (44 %) of title product as colorless amorphous solid.

¹H NMR (270 MHz, CDCl₃) δ 8.28-8.19 (0.5H, m), 7.26-7.10 (6.5H, m), 7.07-7.00 (1H, m), 5.25-5.00 (1H, m), 3.77 (3H, br.s), 3.70-3.40 (1H, m), 3.35-2.80 (8H, m), 2.75-2.50 (1H, m), 2.37-2.20 (2H, m), 2.07-1.40 (4H, m), 1.62-1.50 (2H, m).

33 mg of this solid was dissolved in HCl solution in MeOH (1 ml), concentrated, solidified with CH₂Cl₂/hexane, washed with ether, and collected by filtration to give 29 mg of title compound as white amorphous solid.

¹H NMR (270 MHz, CDCl₃) δ 12.40 (1H, br.s), 8.18 (0.75H, d, J=8.2Hz), 7.43-7.30 (1.25H, m), 7.26-7.15 (5H, m), 7.07 (1H, t, J=7.2Hz), 5.25-5.10 (1H, m), 3.85 (2.25H, s), 3.74 (0.75H, s), 3.72-3.32 (6H, m), 3.20-2.60 (6H, m), 2.07 (2H, t, J=7.1Hz), 1.80-1.50 (4H, m).

MS (ESI positive) m/z: 419 (M+H)⁺.

IR(KBr): 3310, 2934, 2561, 1744, 1655, 1481, 1418, 1207, 758 cm⁻¹

Anal. Calcd for C₂₆H₃₀N₂O₃·HCl·0.8H₂O: C, 66.53; H, 7.00; N, 5.97. Found: C, 66.55; H, 7.00; N, 5.97.

Preparation 4

2,3-Dihydro-1'-[2-(2-hydroxyethoxycarbonyl)ethyl]spiro[1*H*-indene-1,4'-piperidine]

A mixture of 2,3-dihydrospiro[1*H*-indene-1,4'-piperidine] hydrochloride (0.31 g, 1.39 mmol, this was prepared according to known procedure : M. S. Chambers *et al*, *J. Med. Chem.* **1992**, *35*, 2033), ethyl 3-bromopropionate (0.50 g, 2.77 mmol) and *N,N*-diisopropylethylamine (0.54 g, 4.17 mmol) in ethylene glycol (10 ml) was stirred at 80 °C for 16 h. Then the reaction mixture was poured into a saturated aqueous

NaHCO₃ solution, and extracted with AcOEt. The extracts combined were dried (MgSO₄), filtered, and concentrated. The residue was purified by silica gel column chromatography (CH₂Cl₂/MeOH: 20/1 as an eluent) to give 0.37 g (88 %) of title compound as colorless oil.

5 ¹H NMR (300 MHz, CDCl₃) δ 7.25-7.15 (4H, m), 4.37-4.33 (2H, m), 3.84-3.78 (2H, m), 3.01-2.94 (2H, m), 2.94 (2H, t, J=8.1Hz), 2.78-2.72 (2H, m), 2.64-2.58 (2H, m), 2.14-2.05 (2H, m), 2.04-1.91 (4H, m, including 2H, t, J=8.1Hz at 2.00 ppm), 1.60-1.50 (8H, m). MS(EI direct) m/z : 303(M)⁺.

Preparation 5

10 2,3-Dihydro-1'-[2-(carboxy)ethyl]spiro[1*H*-indene-1,4'-piperidine]

A mixture of 2,3-dihydro-1'-[2-(2-hydroxyethoxycarbonyl)ethyl]spiro[1*H*-indene-1,4'-piperidine] (0.37 g, 1.22 mmol), 2N NaOH (4 ml) and EtOH (10 ml) was refluxed with stirring for 16 h. After cooling down to 0 °C, the resulting mixture was neutralized with a 2N HCl solution and extracted with CH₂Cl₂ and AcOEt. The
15 extracts combined were dried (MgSO₄), filtered, and concentrated to give 120 mg (38 %) of title compound as a yellow solid.

¹H NMR (270 MHz, CDCl₃) δ 7.26-7.20 (4H, m), 3.52-3.43 (2H, m), 3.25-3.15 (2H, m), 2.96 (2H, t, J=8.1Hz), 2.91-2.81 (2H, m), 2.70-2.63 (2H, m), 2.33-2.19 (2H, m), 2.08 (2H, t, J=8.1Hz), 1.81-1.70 (2H, m).

20

Example 2

2,3-Dihydro-1'-[3-(indolin-1-yl)-3-oxopropyl]spiro[1*H*-indene-1,4'-piperidine] hydrochloride

A mixture of 2,3-dihydro-1'-[2-(carboxy)ethyl]spiro[1*H*-indene-1,4'-piperidine] (14 mg, 0.054 mmol), indoline (12 µl, 0.108 mmol), WSC (21 mg, 0.108 mmol), HOBt
25 (15 mg, 0.108 mmol), and triethylamine (23 µl, 0.162 mmol) in CH₂Cl₂ (3 ml) was stirred at room temperature overnight. A saturated aqueous NaHCO₃ solution was added to the reaction mixture and aqueous layer was removed by decantation. The separated organic layer was dried (MgSO₄), filtered, and concentrated. The resulting residue was purified by preparative TLC (1 mm thick silica gel plate: CH₂Cl₂/MeOH:10/1) to afford 12 mg (62 %) of colorless oil.
30

¹H NMR (270 MHz, CDCl₃) δ 8.24 (1H, d, J=8.1Hz), 7.24-7.12 (6H, m), 7.05-6.98

(1H, m), 4.10 (2H, t, J=8.4Hz), 3.21 (2H, t, J=8.4Hz), 3.00-2.86 (6H, m), 2.76-2.68 (2H, m), 2.36-2.24 (2H, m), 2.03 (2H, t, J=7.2Hz), 2.03-1.90 (2H, m), 1.63-1.53 (2H, m).

This was converted to HCl salt similar to that described in Example 1 to afford 12 mg
5 of title compound as white solid.

MS (ESI positive) m/z: 361 (M+H)⁺.

Example 3

2,3-Dihydro-1'-[3-(benzimidazol-2-one-1-yl)propyl]spiro[1H-indene-1,4'-piperidine] formate

10 In a one-dram vial were mixed a solution of 1-(3-bromopropyl)benzimidazol-2-one (38 mg, 0.15 mmol, this was reported in EP181793) in ethyleneglycol (1 ml) and a solution of 2,3-dihydrospiro[1H-indene-1,4'-piperidine] hydrochloride (11 mg, 0.05 mmol) and N,N-diisopropylethylamine (17μl, 0.1mmol) in ethyleneglycol (1ml), and the mixture was agitated by shaking at 100°C. After 24 h, the reaction mixture was
15 loaded onto a BondElute[®] SCX cartridge (500 mg /3 ml) which was preconditioned with MeOH (1 ml). The solid-phase matrix was washed with MeOH (5 ml) and then eluted with 2M ammonia/MeOH solution (2 ml). The eluate was concentrated under reduced pressure to give an oil, to which were added CH₂Cl₂ (1 ml) and PS-NCO (1.3 mmol/g; 75 mg, 0.1 mmol). The resulting suspension was shaken at room temperature
20 for 2 h. Insoluble polymers were removed by filtration, and the filtrate was concentrated to dryness by vacuum centrifuge to give an amorphous solid, which was purified with reverse-phase preparatory HPLC (0.1 % HCO₂H-MeOH) to give the title compound as a formic acid salt (6.2 mg; 27% yield).

25 ESI-MS (LC/MS) : Calcd. for C₂₃H₂₇N₃O: [M+H]⁺ = 362.22. Found: 362.58
HPLC purity: 97.8% (UV 210-400nm); retention time: 3.58min

Preparation 6

2,3-Dihydro-1'-(3-hydroxypropyl)spiro[1H-indene-1,4'-piperidine]

A mixture of 2,3-dihydrospiro[1H-indene-1,4'-piperidine] hydrochloride (0.5 g, 2.23
30 mmol, this was prepared according to known procedure : M. S. Chambers *et al*, *J. Med. Chem.* 1992, 35, 2033), 3-bromopropanol (0.3 ml, 3.35 mmol), K₂CO₃ (924.6 mg, 6.69 mmol), and KI (185.9 mg, 1.12 mmol) in MeCN (30 ml) was refluxed with

stirring for 18 h. After cooling down to room temperature, water (30 ml) was added to the reaction mixture and extracted with CH₂Cl₂ (20 ml x 3). The extracts combined were dried (Na₂SO₄), filtered, and concentrated to give 574.7 mg of crude product. This was purified by silica gel column chromatography (CH₂Cl₂/MeOH: 15/1 as an eluent) to afford 288.7 mg (53 %) of title compound as pale yellow white solid.

¹H NMR (270 MHz, CDCl₃) δ 7.26-7.12 (4H, m), 3.86 (2H, t, J=5.3Hz), 3.34-3.24 (2H, m), 2.95-2.88 (4H, m), 2.56-2.42 (2H, m), 2.26-2.10 (2H, m), 2.03 (2H, t, J=7.3Hz), 1.96-1.85 (2H, m), 1.71-1.60 (2H, m).

MS(EI direct) m/z : 245(M)⁺.

10

Preparation 7

2,3-Dihydro-1'-(3-mesyloxypropyl)spiro[1*H*-indene-1,4'-piperidine]

To a stirred solution of 2,3-dihydro-1'-(3-hydroxypropyl)spiro[1*H*-indene-1,4'-piperidine] (288.7 mg, 1.18 mmol) in CH₂Cl₂ (10 ml) was added triethylamine (0.3 ml, 2.12 mmol) followed by dropwise addition of mesyl chloride (0.11 ml, 1.42 mmol) at 0 °C. After 1 h stirring at 0 °C, the reaction mixture was poured into a saturated aqueous NaHCO₃ solution and extracted with CH₂Cl₂ (30 ml x 3). The extracts combined were washed with brine, dried (Na₂SO₄), filtered, and concentrated to give 330.4 mg of title compound as yellow oil, which was used for the next reaction without purification.

¹H NMR (270 MHz, CDCl₃) δ 7.26-7.11 (4H, m), 4.34 (2H, t, J=6.4Hz), 3.03 (3H, s), 2.96-2.80 (4H, m), 2.51 (2H, t, J=7.2Hz), 2.24-2.12 (2H, m), 2.05-1.84 (6H, m), 1.62-1.50 (2H, m).

MS(EI direct) m/z : 323(M)⁺.

Example 4

2,3-Dihydro-1'-[3-(benzothiazol-2-one-1-yl)propyl]spiro[1*H*-indene-1,4'-piperidine] hydrochloride

To a stirred solution of NaH (13.6 mg, 0.34 mmol, 60% oil dispersion in mineral oil, which was removed by washing with n-hexane (2 ml x 2) before use) and benzothiazol-2-one (46.9 mg, 0.31 mmol) in DMF (1 ml) was added a solution of 2,3-dihydro-1'-(3-mesyloxypropyl)spiro[1*H*-indene-1,4'-piperidine] (50 mg, 0.155 mmol) in DMF (1.5 ml) at 0 °C. The reaction mixture was heated to 100 °C with stirring for 21 h. The reaction mixture was cooled to 0 °C and NaHCO₃ solution was added to

30

the reaction mixture, then extracted with CH₂Cl₂ (15 ml x 3). The extracts combined were washed with brine, dried (Na₂SO₄), and filtered. The filtrate was evaporated in vacuo to afford 87 mg of crude product, which was purified by preparative TLC (1 mm thick silica gel plate: CH₂Cl₂/MeOH:20/1, 2 times developed) to give the product. It was purified again by preparative TLC (1 mm thick silica gel plate: n-hexane/AcOEt:2/1, 2 times developed) to give 36.4 mg (62 %) of free form of the title compound as pale yellow oil.

¹H NMR (270 MHz, CDCl₃) δ 7.45-7.41 (1H, m), 7.35-7.28 (1H, m), 7.24-7.12 (6H, m), 4.05 (2H, t, J=6.9Hz), 2.92-2.80 (4H, m), 2.46 (2H, t, J=6.9Hz), 2.19-2.08 (2H, m), 2.04-1.83 (6H, m), 1.58-1.48 (2H, m).

MS (ESI positive) m/z: 379 (M+H)⁺.

This was converted to HCl salt similar to that described in Example 1 to give 24.7 mg of HCl salt as white solid.

IR(KBr): 3416, 2939, 2500, 1678, 1474, 748 cm⁻¹

Anal. Calcd for C₂₃H₂₆N₂OS-HCl-0.4H₂O: C, 65.43; H, 6.64; N, 6.63. Found: C, 65.66; H, 6.81; N, 6.36.

Preparation 8

2,3-Dihydro-1'-[3-(2-carboxyindolin-1-yl)-3-oxopropyl]spiro[1H-indene-1,4'-piperidine]

A mixture of 2,3-dihydro-1'-[3-(2-methoxycarbonylindolin-1-yl)-3-oxopropyl]spiro[1H-indene-1,4'-piperidine] (42 mg, 0.092 mmol, this was prepared in Example 1) and 2N HCl (1 ml) in acetic acid (3 ml) was heated at 90 °C with stirring for 16 h. The reaction mixture was concentrated to give solid which was triturated in AcOEt. The solid was collected by filtration to afford 30 mg as a pale red solid. This showed no methyl singlet peak of methyl ester in starting material in ¹H NMR spectroscopy. This was used for the next reaction without purification.

Example 5

2,3-Dihydro-1'-[3-[2-(N-methylaminocarbonyl)indolin-1-yl]-3-oxopropyl]spiro[1H-indene-1,4'-piperidine] hydrochloride

A mixture of 2,3-dihydro-1'-[3-(2-carboxyindolin-1-yl)-3-oxopropyl]spiro[1H-indene-1,4'-piperidine] (30 mg, 0.068 mmol), methylamine hydrochloride (10 mg, 0.136

mmol), WSC (26 mg, 0.136 mmol), HOBt (19 mg, 0.136 mmol), and triethylamine (47 μ l, 0.34 mmol) in CH₂Cl₂ (4 ml) was stirred at room temperature for 16 h. The reaction mixture was poured into saturated aqueous NaHCO₃ solution, extracted with CH₂Cl₂, dried (MgSO₄), filtered, and concentrated. The residue was purified by preparative TLC (1 mm thick silica gel plate, CH₂Cl₂/MeOH: 10/1) to afford 6 mg (21 %) of free form of the title compound as white solid.

¹H NMR (270 MHz, CDCl₃) δ 8.20 (1H, br.s), 7.26-7.00 (7H, m), 6.40 (1H, br.s), 5.30-4.90 (1H, m), 3.75-3.20 (2H, m), 3.10-2.90 (4H, m), 2.90 (2H, t, J=7.4Hz), 2.79 (3H, d, J=4.8Hz), 2.45-2.25 (4H, m), 2.02 (2H, t, J=7.4Hz), 2.09-1.90 (2H, m), 1.63-1.53 (2H, m).

MS (ESI positive) m/z: 418 (M+H)⁺.

This was converted to HCl salt similar to that described in Example 1 to give 6 mg of HCl salt as a pale gray solid.

MS (ESI positive) m/z: 418 (M+H)⁺.

15

Example 6

2,3-Dihydro-1'-[2-(1,1-dioxido-3-oxo-1,2-benzisotiazol-2(3H)-yl)ethyl]spiro[1H-indene-1,4'-piperidine]

A mixture of 2,3-dihydrospiro[1H-indene-1,4'-piperidine] hydrochloride (80 mg, 0.357 mmol), N-2-(mesyloxy)ethylsaccharin (130.7 mg, 0.428 mmol), K₂CO₃ (148 mg, 1.07 mmol) and KI (29.7 mg, 0.179 mmol) in MeCN (6 ml) was refluxed with stirring for 18 h. After cooling down to room temperature, the reaction mixture was poured into aqueous NaHCO₃ solution and extracted with CH₂Cl₂ (20 ml x 3). The extracts combined were washed with brine, dried (Na₂SO₄), filtered, and concentrated to give 191.7 mg of crude product, which was purified by preparative TLC (1 mm thick silica gel plate, CH₂Cl₂/MeOH: 25/1). Then extracted product was purified again by preparative TLC (n-hexane/AcOEt:1/1, 2 times developed) to give 31.6 mg (22 %) of title compound as pale yellow oil.

¹H NMR (270 MHz, CDCl₃) δ 8.10-8.05 (1H, m), 7.96-7.80 (3H, m), 7.24-7.12 (4H, m), 3.96 (2H, dd, J=7.2, 7.6Hz), 3.04-2.95 (2H, m), 2.89 (2H, t, J=7.4Hz), 2.85 (2H, t, J=7.6Hz), 2.41-2.28 (2H, m), 2.06-1.88 (4H, m), 1.96-1.88 (2H, m).

MS (ESI positive) m/z: 397 (M+H)⁺.

IR(KBr): 2924, 1734, 1327, 1180, 752 cm^{-1}

Anal. Calcd for $\text{C}_{22}\text{H}_{24}\text{N}_2\text{O}_3\text{S}\cdot 0.2\text{H}_2\text{O}$: C, 66.04; H, 6.15; N, 7.00. Found: C, 66.06; H, 6.27; N, 6.73.

Example 7

5 **2,3-Dihydro-1'-[3-(2-oxo-3,4-dihydro-1(2H)-quinolinyl)propyl]spiro[1H-indene-1,4'-piperidine] citrate**

This was prepared according to the procedure described in Example 4 using 3,4-dihydro-2(1H)-quinolinone instead of benzothiazol-2-one. Yield was 38.1 mg (66 %). Product was pale yellow oil.

10 ^1H NMR (270 MHz, CDCl_3) δ 7.28-7.10 (7H, m), 6.99 (1H, ddd, $J=1.2, 7.2, 7.4\text{Hz}$), 4.02 (2H, dd, $J=7.3, 7.6\text{Hz}$), 2.95-2.84 (6H, m), 2.68-2.61 (2H, m), 2.52-2.45 (2H, m), 2.26-2.12 (2H, m), 2.03-1.84 (6H, m), 1.60-1.50 (2H, m).

To a stirred solution of this oil (36.3 mg, 0.097 mmol) in MeOH (1.5 ml) was added citric acid (18.6 mg, 0.097 mmol) at room temperature. After 2 h stirring, the solvent
15 was evaporated to give 45 mg of citric acid salt as white amorphous solid.

MS (ESI positive) m/z : 375 ($\text{M}+\text{H}$) $^+$.

IR(KBr): 3402, 2945, 2600, 1728, 1657, 1601, 1387, 1190, 758 cm^{-1}

Anal. Calcd for $\text{C}_{25}\text{H}_{30}\text{N}_2\text{O}\cdot\text{C}_6\text{H}_8\text{O}_7\cdot\text{H}_2\text{O}$: C, 63.68; H, 6.90; N, 4.79. Found: C, 63.90; H, 6.86; N, 4.63.

20

Example 8

2,3-Dihydro-1'-[3-(3-methyl-2-oxo-3,4-dihydro-1(2H)-quinazolinyl)propyl]spiro[1H-indene-1,4'-piperidine] citrate

This was prepared according to the procedure described in Example 4 using 3,4-dihydro-3-methyl-2(1H)-quinazolinone instead of benzothiazol-2-one. Yield was 28
25 mg (46 %). Product was pale yellow oil.

^1H NMR (270 MHz, CDCl_3) δ 7.28-7.10 (5H, m), 7.08-6.91 (3H, m), 4.37 (2H, s), 3.94 (2H, dd, $J=7.4, 7.6\text{Hz}$), 3.02 (3H, s), 3.01-2.86 (4H, m), 2.58-2.50 (2H, m), 2.29-2.16 (2H, m), 2.06-1.88 (6H, m), 1.62-1.50 (2H, m).

To a stirred solution of this oil (28 mg, 0.072 mmol) in MeOH (1.5 ml) was added
30 citric acid (13.8 mg, 0.072 mmol) at room temperature. After 1 h stirring, the solvent was evaporated to give 36.8 mg of citric acid salt as white amorphous solid.

MS (ESI positive) m/z: 390 (M+H)⁺.

IR(KBr): 3416, 2939, 2600, 1728, 1657, 1641, 1605, 1489, 1213, 758 cm⁻¹

Anal. Calcd for C₂₅H₃₁N₃O-C₆H₈O₇-H₂O: C, 62.09; H, 6.89; N, 7.01. Found: C, 62.26; H, 6.88; N, 6.75.

5

Example 9

2,3-Dihydro-1'-[3-(2-oxo-1,3-benzoxazol-3(2H)-yl)propyl]spiro[1H-indene-1,4'-piperidine] citrate

This was prepared according to the procedure described in Example 4 using benzoxazol-2-one instead of benzothiazol-2-one. Yield was 29.4 mg (52 %). Product
10 was reddish brown oil.

¹H NMR (300 MHz, CDCl₃) δ 7.26-7.06 (8H, m), 3.94 (2H, t, J=6.8Hz), 2.88 (2H, t, J=7.3Hz), 2.45 (2H, t, J=6.8Hz), 2.16-2.06 (2H, m), 2.05-1.94 (4H, m), 1.90-1.78 (2H, m), 1.55-1.47 (2H, m).

To a stirred solution of this oil (29.4 mg, 0.081 mmol) in MeOH (1.5 ml) was added
15 citric acid (15.6 mg, 0.081 mmol) at room temperature. After 1 h stirring, the solvent was evaporated to give 32.5 mg of citric acid salt as red amorphous solid.

MS (ESI positive) m/z: 363 (M+H)⁺.

IR(KBr): 3437, 2939, 2544, 1771, 1732, 1589, 1487, 1371, 1254, 756 cm⁻¹

Anal. Calcd for C₂₃H₂₆N₂O₂-C₆H₈O₇-0.5H₂O: C, 61.80; H, 6.26; N, 4.97. Found:
20 C, 61.41; H, 6.24; N, 4.88.

Example 10

2,3-Dihydro-1'-[3-(2-carboxyindolin-1-yl)-3-oxopropyl]spiro[1H-indene-1,4'-piperidine]

To a stirred solution of 2,3-dihydro-1'-[3-(2-methoxycarbonylindolin-1-yl)-3-oxopropyl]spiro[1H-indene-1,4'-piperidine] (125 mg, 0.3 mmol, this was prepared in
25 Example 1) in THF (3 ml) and MeOH (1 ml) was added 2N NaOH (0.6 ml, 1.2 mmol) at room temperature. After 16 h stirring at room temperature, the reaction mixture was neutralized with 2N HCl (0.6 ml) and 4 drops of saturated aqueous NaHCO₃ solution, diluted with water (5 ml), and extracted with CH₂Cl₂. The extracts combined were
30 dried (MgSO₄), filtered, and concentrated to give 105 mg (87 %) of title product as white solid.

¹H NMR (270 MHz, DMSO-*d*₆) δ 8.09 (1H, d, J=8.4Hz), 7.30-6.80 (8H, m), 5.35-5.15 (1H, m), 3.70-2.75 (12H, m), 2.10-1.95 (4H, m), 1.70-1.55 (2H, m).

MS (ESI positive) m/z: 405 (M+H)⁺.

Example 11

5 **2,3-Dihydro-1'-[3-(2-*N,N*-dimethylaminocarbonylindolin-1-yl)-3-oxopropyl]spiro[1*H*-indene-1,4'-piperidine] hydrochloride**

A mixture of 2,3-dihydro-1'-[3-(2-carboxyindolin-1-yl)-3-oxopropyl]spiro[1*H*-indene-1,4'-piperidine] (23 mg, 0.057 mmol, this was prepared in Example 10), dimethylamine hydrochloride (14 mg, 0.17 mmol), WSC (22 mg, 0.114 mmol), HOBt
10 (16 mg, 0.114 mmol), and triethylamine (40 μl, 0.29 mmol) in CH₂Cl₂ (3 ml) was stirred at room temperature for 20 h. The reaction mixture was diluted with saturated aqueous NaHCO₃ solution and extracted with CH₂Cl₂. The extracts combined were dried (MgSO₄), filtered, and concentrated. The residue was purified by preparative TLC (1 mm thick plate, CH₂Cl₂/MeOH: 10/1) to give 20 mg (81 %) of free form of
15 title product as colorless oil.

¹H NMR (270 MHz, CDCl₃) δ 8.29 (0.5H, d, J=7.9Hz), 7.65-6.95 (7.5H, m), 5.50-5.40 (0.5H, m), 5.35-5.25 (0.5H, m), 3.77-3.60 (0.5H, m), 3.53-3.35 (0.5H, m), 3.22-2.20 (17H, m, including 1.5H, s at 3.19 ppm, 1.5H, s at 3.16 ppm, 1.5H, s at 3.01 ppm, 1.5H, s at 2.98 ppm, 2H, t, J=7.4Hz at 2.90 ppm), 2.15-1.90 (4H, m, including 2H, t, J=7.4Hz at 2.02 ppm), 1.75-1.50 (2H, m).
20

This was converted to HCl salt similar to that described in Example 1 to give 15 mg of HCl salt as a white solid.

¹H NMR (270 MHz, CDCl₃) δ 12.13 (1H, br.s), 8.25 (1H, d, J=8.2Hz), 7.40-7.00 (7H, m), 5.65-5.50 (1H, m), 3.85-2.50 (18H, m including 3H, s at 3.28 ppm, 3H, s at 3.05
25 ppm, and 2H, t, J=7.4Hz at 2.95 ppm), 2.04 (2H, t, J=7.4Hz), 1.80-1.50 (4H, m).

MS (ESI positive) m/z: 432 (M+H)⁺.

IR(KBr): 3446, 2936, 2561, 1653, 1483, 1458, 1398, 1271, 758 cm⁻¹

Anal. Calcd for C₂₇H₃₃N₃O₂·HCl·H₂O: C, 66.72; H, 7.47; N, 8.65. Found: C, 66.48; H, 7.48; N, 8.56.

30

Example 12

2,3-Dihydro-1'-[3-(2-morpholinocarbonylindolin-1-yl)-3-oxopropyl]spiro[1*H*-

indene-1,4'-piperidine] hydrochloride

This was prepared according to the procedure described in Example 11 using morpholine instead of dimethylamine hydrochloride. 23 mg (86 %) of free form of title compound was obtained as colorless oil.

- 5 ^1H NMR (270 MHz, CDCl_3) δ 8.35-8.23 (0.4H, m), 7.33-7.05 (6.6H, m), 7.01 (1H, br.dd, $J=7.4, 8.4\text{Hz}$), 5.50-5.40 (0.6H, m), 5.37-5.25 (0.4H, m), 3.90-3.35 (9H, m), 3.13-2.20 (11H, m, including 2H, t, $J=7.5\text{Hz}$ at 2.90ppm), 2.10-1.90 (4H, m, including 2H, t, $J=7.4\text{Hz}$ at 2.02 ppm), 1.65-1.50 (2H, m).

- This was converted to HCl salt similar to that described in Example 1 to give 18 mg of
10 HCl salt as a white solid.

^1H NMR (270 MHz, CDCl_3) δ 8.25 (1H, d, $J=7.9\text{Hz}$), 7.40-7.00 (8H, m), 5.80-5.70 (1H, m), 4.08-3.35 (13H, m), 3.13-2.50 (7H, m, including 2H, t, $J=7.4\text{Hz}$ at 2.95ppm), 2.04 (2H, t, $J=7.6\text{Hz}$), 1.80-1.50 (4H, m).

MS (ESI positive) m/z : 474 ($\text{M}+\text{H}$) $^+$.

- 15 IR(KBr): 2928, 2550, 1655, 1119, 752 cm^{-1}

Anal. Calcd for $\text{C}_{29}\text{H}_{35}\text{N}_3\text{O}_3\cdot\text{HCl}\cdot 0.7\text{H}_2\text{O}$: C, 66.64; H, 7.21; N, 8.04. Found: C, 66.85; H, 7.32; N, 7.89.

Example 13

- 2,3-Dihydro-1'-[3-[2-(aminocarbonyl)-2,3-dihydro-1H-indol-1-yl]-3-oxopropyl]spiro[1H-indene-1,4'-piperidine] hydrochloride**
20

- To a stirred suspension of 2,3-dihydro-1'-[3-(2-carboxyindolin-1-yl)-3-oxopropyl]spiro[1H-indene-1,4'-piperidine] (20 mg, 0.049 mmol, this was prepared in Example 10) in MeCN (4 ml) was added 1,1'-carbonyldiimidazole (9 mg, 0.054 mmol) at room temperature and resulting mixture was refluxed for 0.5 h.
- 25 Triethylamine (10 μl) was added to the reaction mixture and reflux was continued for 2 h. To a reaction mixture was added 25 % NH_4OH (2 ml) and reflux was continued for 2 h. Then the reaction mixture was concentrated, diluted with saturated aqueous NaHCO_3 solution, and extracted with CH_2Cl_2 . The extracts combined were dried (MgSO_4), filtered, and concentrated. The residue was purified by preparative TLC (1
30 mm thick plate, $\text{CH}_2\text{Cl}_2/\text{MeOH}$: 10/1) to afford 9 mg (45 %) of free form of title compound as colorless amorphous solid.

This compound showed broadened spectra in proton NMR.

This was converted to HCl salt similar to that described in Example 1 to give 8 mg of HCl salt as a white solid.

¹H NMR (270 MHz, CDCl₃ + CD₃OD) δ 8.17 (1H, d, J = 7.6 Hz), 7.38-7.03 (8H, m),
5 5.35-5.10 (1H, m), 3.85-3.20 (10H, m), 3.15-2.35 (6H, m, including 2H, t, J = 7.3 Hz
at 3.00 ppm), 2.10 (2H, t, J = 7.3 Hz), 1.83-1.70 (2H, m).

MS (ESI positive) m/z: 404 (M+H)⁺.

Example 14

2,3-Dihydro-1'-[3-(2-(S)-methoxycarbonylindolin-1-yl)-3-oxopropyl]spiro[1H- 10 indene-1,4'-piperidine] hydrochloride

To a stirred suspension of (2S)-methyl indoline-2-carboxylate hydrochloride (520 mg, 2.43 mmol) in CH₂Cl₂ (10 ml) was added triethylamine (1.13 ml, 8.1 mmol) at 0 °C. After 10 minutes stirring, 2,3-dihydro-1'-[2-(chloroformyl)ethyl]spiro[1H-indene-1,4'-
15 piperidine] hydrochloride (510 mg, 1.62 mmol) was added to the reaction mixture at
0 °C and the resulting reaction mixture was stirred at 0 °C for 4 h. The reaction
mixture was quenched with a saturated aqueous NaHCO₃ solution and extracted with
CH₂Cl₂. The extracts combined were washed with brine, dried (MgSO₄), filtered, and
concentrated. The residue was purified by silica gel column chromatography
(CH₂Cl₂/MeOH: 20/1 as an eluent) to give 345 mg (49 %) of colorless amorphous
20 solid.

¹H NMR (270 MHz, CDCl₃) δ 8.30-8.15 (0.5H, m), 7.35-7.07 (6.5H, m), 7.05-6.95
(1H, m), 5.25-4.98(1H, m), 3.74 (3H, br.s), 3.70-3.35 (1H, m), 3.35-2.45 (9H, m),
2.35-2.15 (2H, m), 2.05-1.85 (4H, m), 1.65-1.48 (2H, m).

24 mg of this solid was dissolved in HCl solution in MeOH (0.5 ml), concentrated,
25 solidified with ether, and collected by filtration to give 22 mg of title compound as
white amorphous solid.

MS (ESI positive) m/z: 419 (M+H)⁺.

IR(KBr): 3420, 2951, 2563, 1744, 1661, 1481, 1418, 1207, 758 cm⁻¹

Anal. Calcd for C₂₆H₃₀N₂O₃-HCl-0.6H₂O: C, 67.04; H, 6.97; N, 6.01. Found: C,
30 67.07; H, 7.10; N, 5.78.

Example 15**2,3-Dihydro-1'-{3-[2-(1-ethylpyrrolydin-3-yl)aminocarbonylindolin-1-yl]-3-oxopropyl}spiro[1*H*-indene-1,4'-piperidine] dihydrochloride**

A mixture of 2,3-dihydro-1'-[3-(2-carboxyindolin-1-yl)-3-oxopropyl]spiro[1*H*-indene-1,4'-piperidine] (35 mg, 0.087 mmol, this was prepared in Example 10), 3-amino-1-benzylpyrrolidine (31 mg, 0.17 mmol), WSC (33 mg, 0.17 mmol), HOBt (23 mg, 0.17 mmol), and triethylamine (36 μ l, 0.26 mmol) in CH₂Cl₂ (4 ml) was stirred at room temperature for 18 h. The reaction mixture was diluted with saturated aqueous NaHCO₃ solution and extracted with CH₂Cl₂. The extracts combined were dried (MgSO₄), filtered, and concentrated. The residue was purified by preparative TLC (1 mm thick plate, CH₂Cl₂/MeOH: 7/1) to give 28 mg (57 %) of amide product as colorless oil.

MS (ESI positive) m/z: 563 (M+H)⁺.

A suspension mixture of this oil (28 mg, 0.05 mmol), 10 % palladium on activated carbon (10 mg) and EtOH (6 ml) was stirred under hydrogen atmosphere at room temperature for 24 h. Then 5 mg of 10 % palladium on activated carbon was added to the reaction mixture and continued the hydrogenation for 24 h. After the removal of the catalyst by filtration, the filtrate was concentrated. The resulting crude oil was purified by preparative TLC (1 mm thick plate, CH₂Cl₂/MeOH: 7/1) to give 15 mg (64 %) of pale brown oil as free form of title compound. This compound showed broadened spectra in proton NMR. This was converted to HCl salt similar to that described in Example 1 to give 15 mg of HCl salt as a white solid.

MS (ESI positive) m/z: 501 (M+H)⁺.

Example 16**2,3-Dihydro-1'-[3-(indol-1-yl)-3-oxopropyl]spiro[1*H*-indene-1,4'-piperidine] citrate**

To a stirred suspension of 2,3-dihydro-1'-[2-(chloroformyl)ethyl]spiro[1*H*-indene-1,4'-piperidine] hydrochloride (100 mg, 0.32 mmol), indole (75 mg, 0.64 mmol), tetrabutylammonium hydrogen sulfate (54 mg, 0.16 mmol) and powdered NaOH (51 mg, 1.28 mmol) in CH₂Cl₂ (4 ml) was added triethylamine (67 μ l, 0.48 mmol) at room temperature. After 45 minutes stirring, the reaction mixture was quenched with a saturated aqueous NaHCO₃ solution and extracted with CH₂Cl₂. The extracts

combined were washed with brine, dried (MgSO₄), filtered, and concentrated. The residue was purified by preparative TLC (1 mm thick plate, CH₂Cl₂/MeOH: 10/1, then purified again using 0.5 mm thick plate, ethyl acetate) to give 7 mg (6 %) of colorless oil.

5 ¹H NMR (270 MHz, CDCl₃) δ 8.47 (1H, d, J = 8.2 Hz), 7.57 (1H, d, J = 8.2 Hz), 7.51 (1H, d, J = 3.8 Hz), 7.40-7.12 (6H, m), 6.66 (1H, d, J = 3.8 Hz), 3.20 (2H, t, J = 6.9 Hz), 3.06-2.87 (6H, m), 2.40-2.28 (2H, m), 2.07-1.91 (4H, m), 1.64-1.54 (2H, m).

7 mg (0.02 mmol) of this oil and citric acid (3.8 mg, 0.02 mmol) was dissolved in CH₂Cl₂ (1 ml) and MeOH (1 ml) mixture. After 1 h stirring, the mixture solution was
10 concentrated, solidified with ether, and collected by filtration to give 6 mg of title compound as white amorphous solid.

MS (ESI positive) m/z: 359 (M+H)⁺.

Preparation 9

2,3-Dihydro-1'-[3-(2-(S)-carboxyindolin-1-yl)-3-oxopropyl]spiro[1*H*-indene-1,4'-piperidine]
15

This was prepared according to the procedure described in Example 10 using 2,3-dihydro-1'-[3-(2-(S)-methoxycarbonylindolin-1-yl)-3-oxopropyl]spiro[1*H*-indene-1,4'-piperidine] instead of 2,3-dihydro-1'-[3-(2-methoxycarbonylindolin-1-yl)-3-oxopropyl]spiro[1*H*-indene-1,4'-piperidine]. 300 mg (100 %) of title compound was
20 obtained as white solid.

¹H NMR (270 MHz, CDCl₃) δ 8.22 (1H, d, J=7.9Hz), 7.24-7.08 (6H, m), 7.04-6.97 (1H, m), 6.94-6.86 (1H, m), 5.06-4.97 (1H, m), 3.70-3.06 (8H, m), 3.00-2.76 (4H, m), 2.33-2.13 (2H, m), 2.06-1.94 (2H, m), 1.68-1.44 (2H, m).

MS (ESI positive) m/z: 405 (M+H)⁺.

25

Example 17

2,3-Dihydro-1'-{3-[2-(S)-[[[2-(dimethylamino)ethyl]amino]carbonyl]indolin-1-yl]-3-oxopropyl}spiro[1*H*-indene-1,4'-piperidine] dicitrate

A mixture of 2,3-dihydro-1'-[3-(2-(S)-carboxyindolin-1-yl)-3-oxopropyl]spiro[1*H*-indene-1,4'-piperidine] (50 mg, 0.124 mmol, this was prepared in Preparation 9), *N,N*-dimethylethylenediamine (41 μl, 0.37 mmol), WSC (48 mg, 0.25 mmol), HOBt (34
30 mg, 0.25 mmol), and triethylamine (86 μl, 0.62 mmol) in CH₂Cl₂ (3 ml) was stirred at

room temperature for 18 h. The reaction mixture was diluted with saturated aqueous NaHCO₃ solution and extracted with CH₂Cl₂. The extracts combined were dried (MgSO₄), filtered, and concentrated. The residue was purified by preparative TLC (1 mm thick plate, CH₂Cl₂/MeOH: 5/1) to give 37 mg (63 %) of free form of title compound as colorless oil. This compound showed broadened spectra in proton NMR. This oil was converted to citric acid salt by mixing with 2 equivalent of citric acid in mixed solvent of CH₂Cl₂-MeOH followed by concentration.

MS (ESI positive) m/z: 475 (M+H)⁺.

IR(KBr): 3398, 2941, 2712, 1728, 1655, 1595, 1483, 1418, 1215, 760 cm⁻¹

Anal. Calcd for C₂₉H₃₈N₄O₂-2C₆H₈O₇-H₂O: C, 56.16; H, 6.44; N, 6.39. Found: C, 55.82; H, 6.44; N, 6.22.

Preparation 10

2,3-Dihydro-1'-(3-phthalimidopropyl)spiro[1*H*-indene-1,4'-piperidine]

This was prepared according to the procedure described in Preparation 6 using *N*-(3-bromopropyl)phthalimide instead of 3-bromopropanol. 1184 mg (71 %) of title compound was obtained as yellow solid.

¹H NMR (270 MHz, CDCl₃) δ 7.91-7.83 (2H, m), 7.77-7.70 (2H, m), 7.20-7.08 (3H, m), 6.97-6.88 (1H, m), 3.80 (2H, t, J = 6.8 Hz), 2.88-2.78 (4H, m), 2.47 (2H, t, J = 6.9 Hz), 2.11-2.00 (2H, m), 1.98-1.88 (4H, m), 1.74-1.60 (2H, m), 1.48-1.38 (2H, m).

MS (EI, direct) m/z: 374 (M)⁺.

Preparation 11

2,3-Dihydro-1'-[3-(2-nitroanilino)propyl]spiro[1*H*-indene-1,4'-piperidine]

A mixture of 2,3-dihydro-1'-(3-phthalimidopropyl)spiro[1*H*-indene-1,4'-piperidine] (1.184 g, 3.16 mmol, this was prepared in preparation 10) and hydrazine hydrate (0.348 g, 6.95 mmol) in MeOH (35 ml) was refluxed with stirring for 2 h. After concentration, the reaction mixture was diluted with aqueous NaHCO₃ solution (80 ml) and extracted with CH₂Cl₂ (50 ml x 3). The extracts combined were washed with water (50 ml), dried (Na₂SO₄), filtered, and concentrated to give 381.4 mg (crude yield was 49 %) of amine derivative as yellow oil.

¹H NMR (270 MHz, CDCl₃) δ 7.23-7.10 (4H, m), 2.93-2.55 (6H, m), 2.50-2.41 (2H, m), 2.20-2.08 (2H, m), 2.05-1.88 (4H, m), 1.75-1.63 (2H, m), 1.60-1.50 (2H, m),

1.40 (2H, br.s).

A mixture of above amine derivative (607 mg, 2.48 mmol), 2-fluoronitrobenzene (0.39 ml, 3.72 mmol), and K₂CO₃ (514 mg, 3.72 mmol) in MeCN (10 ml) was refluxed with stirring for 16 h. 0.26 ml (2.48 mmol) of 2-fluoronitrobenzene and 342.8 mg (2.48 mmol) of K₂CO₃ was added to the reaction mixture and reflux was continued for 5 h. The reaction mixture was diluted with water (30 ml) and extracted with CH₂Cl₂ (40 ml x 3). The extracts combined were dried (Na₂SO₄), filtered, and concentrated to give 1356 mg of crude product which was purified by silica gel column chromatography (n-hexane/acetone: 4/1) to afford 836 mg (92 %) of title compound as yellow oil.

¹H NMR (270 MHz, CDCl₃) δ 8.32 (1H, br.s), 8.18 (1H, dd, J = 1.5, 8.4 Hz), 7.47-7.39 (1H, m), 7.30-7.12 (4H, m), 6.91 (1H, br.d, J = 8.4 Hz), 6.63 (1H, ddd, J = 1.2, 7.2, 8.4 Hz), 3.46-3.37 (2H, m), 2.96-2.86 (4H, m), 2.53 (2H, t, J = 6.8 Hz), 2.23-2.12 (2H, m), 2.07-1.88 (6H, m), 1.60-1.50 (2H, m).

Example 18

2,3-Dihydro-1'-[3-(2-hydroxymethylbenzimidazol-1-yl)-3-oxopropyl]spiro[1H-indene-1,4'-piperidine] citrate

To a stirred solution of nitroaniline derivative (836.3 mg, 2.29 mmol, this was prepared in preparation 11) in mixed solvent of MeOH (4.8 ml), THF (14.4 ml), and water (1.2 ml) was added NH₄Cl (367 mg, 6.9 mmol) and Zn powder (1048 mg, 16 mmol) at 0 °C and resulting reaction mixture was stirred at room temperature for 1.5 h. After Celite filtration, the filtrate was concentrated. The resulting residue was diluted with aqueous NaHCO₃ solution (50 ml), extracted with CH₂Cl₂ (40 ml x 4). The extracts combined were washed with brine, dried (Na₂SO₄), filtered, and concentrated to give 797.9 mg of crude phenylenediamine derivative as reddish brown oil.

¹H NMR (270 MHz, CDCl₃) δ 7.24-7.10 (4H, m), 6.88-6.63 (4H, m), 3.43 (1H, br.s), 3.22 (2H, t, J = 6.3 Hz), 3.03-2.94 (2H, m), 2.90 (2H, t, J = 7.4 Hz), 2.58 (2H, t, J = 6.4 Hz), 2.24-2.11 (2H, m), 2.07-1.84 (8H, m), 1.62-1.50 (2H, m).

A mixture of this phenylenediamine derivative (50.3 mg, 0.15 mmol) and glycolic acid (22.8 mg, 0.3 mmol) in 4N HCl (3 ml) was refluxed with stirring for 22.5 h. After cool down to room temperature, the reaction mixture was basified with aqueous 25 % NH₃ solution and extracted with CH₂Cl₂ (20 ml x 3). The extracts combined were washed

with water, dried (Na₂SO₄), filtered, and concentrated to give 51.6 mg of crude product, which was purified by preparative TLC (CH₂Cl₂/MeOH: 15/1, 3 times developed) to afford 25.8 mg of product. As this included some impurity, this was purified again by preparative TLC (AcOEt/i-PrOH/25%NH₃: 50/10/1) to give 18.8 mg (33 %) of free form of title product as pale yellow oil.

¹H NMR (270 MHz, CDCl₃) δ 7.79-7.70 (1H, m), 7.44-7.36 (1H, m), 7.31-7.15 (6H, m), 5.01 (2H, s), 4.48 (2H, t, J = 6.3 Hz), 3.43 (1H, br.s), 2.87 (2H, t, J = 7.3 Hz), 2.82-2.72 (2H, m), 2.34-1.89 (11H, m), 1.57-1.45 (2H, m).

This oil was converted to citric acid salt by mixing with 1 equivalent of citric acid in MeOH (1.5 ml) followed by concentration.

MS (ESI positive) m/z: 376 (M+H)⁺.

IR(KBr): 3396, 2937, 2600, 1717, 1589, 1458, 1209, 1045, 758 cm⁻¹

Anal. Calcd for C₂₄H₂₉N₃O-C₆H₈O₇-2H₂O: C, 59.69; H, 6.85; N, 6.96. Found: C, 59.90; H, 6.51; N, 6.56.

Example 19

2,3-Dihydro-1'-[3-(2-hydroxymethylindolin-1-yl)-3-oxopropyl]spiro[1H-indene-1,4'-piperidine] citrate

This was prepared according to the procedure described in Example 1 using 2-hydroxymethylindoline instead of methyl indoline 2-carboxylate. 126.3 mg (55.9 %) of free base as amorphous solid.

This compound showed broadened spectra in proton NMR except for the following peaks.

¹H NMR (300 MHz, CDCl₃) δ 2.89 (2H, t, J = 7.3 Hz), 2.40-2.15 (2H, m), 2.05-1.80 (4H, m, including 2H, t, J = 7.3 Hz at 2.00 ppm), 1.60-1.45 (2H, m).

This solid was converted to citric acid salt by mixing with 1 equivalent of citric acid in mixed solvent of CH₂Cl₂ and MeOH, followed by concentration to afford the title product.

¹H NMR (270 MHz, DMSO-*d*₆) δ 8.00 (1H, br.d, J=7.3 Hz), 7.30-7.12 (6H, m), 7.03 (1H, br.t, J=7.3 Hz), 4.70-4.55 (1H, m), 3.55-2.75 (14H, m, including 2H, t, J = 7.1 Hz at 2.89 ppm), 2.63 (2H, d, J = 15.2 Hz), 2.53 (2H, d, J = 14.5 Hz), 2.13-1.95 (4H, m, including 2H, t, J = 7.1 Hz at 2.06 ppm), 1.70-1.60 (2H, m).

MS (ESI positive) m/z : 391 ($M+H$)⁺.

IR(KBr): 3350, 2941, 2600, 1728, 1641, 1595, 1481, 1420, 1211, 758 cm⁻¹

Anal. Calcd for C₂₅H₃₀N₂O₂-C₆H₈O₇-2H₂O: C, 60.18; H, 6.84; N, 4.53. Found: C, 60.52; H, 6.49; N, 4.49.

5

Example 20

2,3-Dihydro-1'-[3-(2-methoxymethylindolin-1-yl)-3-oxopropyl]spiro[1*H*-indene-1,4'-piperidine] hydrochloride

To a stirred mixture of 2,3-dihydro-1'-[3-(2-hydroxymethylindolin-1-yl)-3-oxopropyl]spiro[1*H*-indene-1,4'-piperidine] (23.7 mg, 0.0607 mmol) and fluobolic acid (48 % solution in water, 8.7 μl, 0.0668 mmol) in CH₂Cl₂ (2 ml) was added dropwise trimethylsilyldiazomethane (2 M solution in hexane, 30.3 μl, 0.0668 mmol) at 0 °C and stirred for 1 h. Then fluobolic acid (48 % solution in water, 8.7 μl, 0.0668 mmol) and trimethylsilyldiazomethane (2 M solution in hexane, 30.3 μl, 0.0668 mmol) were added to the reaction mixture and stirred at room temperature for 1 h. The reaction mixture was quenched with water and extracted with CH₂Cl₂. The extracts combined were dried (Na₂SO₄), filtered, and concentrated. The residue was purified by preparative TLC (acetone/hexane: 1/1) to give 11.2 mg (45.5 %) of free form of title compound as an yellow oil.

¹H NMR (300 MHz, CDCl₃) δ 8.13 (1H, br.s), 7.25-7.12 (6H, m), 7.04 (1H, dd, J = 7.5, 8.4 Hz), 4.65 (1H, br.s), 3.50-3.25 (5H, m, including 3H, s, at 3.31 ppm), 3.03-2.75 (10H, m, including 2H, t, J = 7.3 Hz at 2.90 ppm), 2.36-2.24 (2H, m), 2.06-1.93 (4H, m, including 2H, t, J = 7.3 Hz at 2.03 ppm), 1.63-1.54 (2H, m).

This was converted to HCl salt similar to that described in Example 1 to give 12.2 mg of HCl salt as a white solid.

MS (ESI positive) m/z : 405 ($M+H$)⁺.

IR(KBr): 3400, 2900, 2600, 1649, 1597, 1481, 1460, 1420, 1275, 1119, 758 cm⁻¹

Example 21

2,3-Dihydro-1'-{3-[2-(S)-(2-hydroxyethyl)aminocarbonylindolin-1-yl]-3-oxopropyl}spiro[1*H*-indene-1,4'-piperidine] hydrochloride

This was prepared according to the procedure described in Example 17 using 2-hydroxyethylamine instead of *N,N*-dimethylethylenediamine and additionally DMF

was added as solvent. Solvent ratio of CH₂Cl₂/THF/DMF was 2/2/1. 10.1 mg (30.4 %) of free form of title compound was obtained as amorphous solid.

¹H NMR (270 MHz, CDCl₃) δ 8.17 (1H, br.s), 7.26-6.80 (8H, m), 4.94 (1H, br.s), 3.75-2.50 (15H, m), 2.45-2.20 (2H, m), 2.07-1.85 (4H, m, including 2H, t, J = 7.1 Hz at 2.01 ppm), 1.63-1.50 (2H, m).

This was converted to HCl salt similar to that described in Example 1 to give 12.2 mg of HCl salt as a white solid.

MS (ESI positive) m/z: 448 (M+H)⁺.

IR(KBr): 3400, 2934, 2700, 1655, 1597, 1481, 1460, 1420, 1271, 1067, 758 cm⁻¹

10

Example 22

2,3-Dihydro-1'-[3-(2-aminomethylindolin-1-yl)-3-oxopropyl]spiro[1H-indene-1,4'-piperidine] hydrochloride

A mixture of 2,3-dihydro-1'-[3-(2-hydroxymethylindolin-1-yl)-3-oxopropyl]spiro[1H-indene-1,4'-piperidine] (this was prepared in Example 19, 37.5 mg, 0.096 mmol), phthalimide (56.5 mg, 0.384 mmol), *N,N,N',N'*-tetramethylazodicarboxamide (66.1 mg, 0.384 mmol) and tributylphosphine (95.7 μl, 0.384 mmol) in THF (2 ml) was stirred at room temperature for 1 day. The reaction mixture was concentrated and the residue was purified by preparative TLC (1 mm thick plate x 2, CH₂Cl₂/MeOH: 10:1) to give 106 mg of brown oil. This was purified again by preparative TLC (1 mm thick plate x 2, AcOEt/i-PrOH/NH₃ solution in EtOH: 100/5/2) to give 57.5 mg of phthalimide derivative as brown oil. A mixture of this oil (57.5 mg) and hydrazine hydrate (18.7 μl, 0.384 mmol) in MeOH (3 ml) was refluxed with stirring for 4 h. After cool down to room temperature, the reaction mixture was concentrated. The resultant solid appeared was removed by filtration. The filtrate was concentrated and the residue was purified by silica gel column chromatography (EtOAc/hexane: 1/5) to give 13.1 mg (35 %) of free form of title compound.

¹H NMR (270 MHz, CDCl₃) δ 8.90-8.75 (1H, m), 7.25-6.95 (5H, m), 6.72-6.65 (1H, m), 6.60 (1H, d, J = 7.8 Hz), 4.16-4.05 (1H, m), 3.52-3.45 (2H, m), 3.25-3.13 (1H, m), 2.95-2.75 (4H, m), 2.60-2.50 (2H, m), 2.42-2.35 (2H, m), 2.22-2.09 (2H, m), 1.99 (2H, t, J = 7.4 Hz), 1.92-1.77 (2H, m), 1.63-1.35 (5H, m).

This was converted to HCl salt similar to that described in Example 1 to give 13.1 mg of HCl salt as a white solid.

MS (ESI positive) m/z : 390 ($M+H$)⁺.

IR(KBr): 3420, 3269, 2930, 2575, 2480, 1655, 1545, 1466, 1248, 756 cm^{-1}

Example 23

5 **2,3-Dihydro-1'-{3-[2-(S)-(2-aminoethyl)aminocarbonylindolin-1-yl]-3-oxopropyl}spiro[1*H*-indene-1,4'-piperidine] dihydrochloride**

This was prepared according to the procedure described in Example 21 using 2-*t*-butoxycarbonylaminoethylamine instead of 2-hydroxyethylamine followed by removal of Boc group by treatment of HCl solution in MeOH and basic workup. 18.1 mg (53.1 %) of free base was obtained as white amorphous solid.

10 This compound showed broadened spectra in proton NMR except for the following peaks.

¹H NMR (300 MHz, CDCl₃) δ 2.90 (2H, t, $J = 7.2$ Hz), 2.01 (2H, t, $J = 7.3$ Hz), 1.63-1.50 (2H, m).

This was converted to HCl salt similar to that described in Example 1 to give 18 mg of
15 HCl salt as a white solid.

¹H NMR (300 MHz, DMSO-*d*₆) δ 10.50 (1H, br.s), 8.75 (1H, br.s), 8.25-7.85 (4H, m, including 1H, d, $J = 7.9$ Hz), 7.35-7.00 (7H, m), 5.20-5.12 (1H, m), 3.75-2.70 (16H, m), 2.35-2.15 (2H, m), 2.09 (2H, t, $J = 7.2$ Hz), 1.73-1.62 (2H, m).

MS (ESI positive) m/z : 447 ($M+H$)⁺.

20 IR(KBr): 3400, 3236, 2941, 2700, 2575, 1655, 1597, 1541, 1481, 1462, 1416, 1269, 970, 758 cm^{-1} .

Anal. Calcd for C₂₇H₃₄N₄O₂·2HCl·2.9H₂O: C, 56.72; H, 7.37; N, 9.80. Found: C, 56.97; H, 7.35; N, 9.75.

Example 24

25 **2,3-Dihydro-1'-{3-[2-(S)-(2-acetamidoethyl)aminocarbonylindolin-1-yl]-3-oxopropyl}spiro[1*H*-indene-1,4'-piperidine] hydrochloride**

A mixture of 2,3-dihydro-1'-{3-[2-(S)-(2-aminoethyl)aminocarbonylindolin-1-yl]-3-oxopropyl}spiro[1*H*-indene-1,4'-piperidine] (this was prepared in Example 23, 55 mg, 0.053 mmol), acetic anhydride (15.1 μ l, 0.16 mmol), and 4-dimethylaminopyridine
30 (1.3 mg, 0.011 mmol) in pyridine (3 ml) was stirred at room temperature for 4 h. After evaporation of the pyridine, the residue was diluted with 2N HCl and CH₂Cl₂. The mixture was extracted with CH₂Cl₂. The extracts combined were washed with

saturated aqueous NaHCO₃ solution and brine, dried (Na₂SO₄), filtered, and concentrated. The residue was purified by preparative TLC (CH₂Cl₂/MeOH:10/1) to give 23.2 mg (89.2 %) of free base as amorphous solid.

This compound showed broadened spectra in proton NMR except for the following peaks.

¹H NMR (270 MHz, CDCl₃) δ 7.06 (1H, dd, J = 7.0, 7.3 Hz), 2.92 (2H, t, J = 7.4 Hz), 2.03 (2H, t, J = 7.4 Hz), 1.75-1.50 (2H, m).

This was converted to HCl salt similar to that described in Example 1 to give 23 mg of HCl salt as a white solid.

¹H NMR (300 MHz, DMSO-*d*₆) δ 8.52 (1H, br.s), 8.08 (1H, d, J = 7.9 Hz), 7.30-6.95 (8H, m), 5.13-5.05 (1H, m), 3.65-2.45 (17H, m), 2.30-2.00 (4H, m), 1.82 (3H, s), 1.75-1.60 (2H, m).

MS (ESI positive) m/z: 489 (M+H)⁺.

IR(KBr): 3400, 3267, 2936, 2700, 2573, 1655, 1545, 1481, 1416, 1246, 746 cm⁻¹.

Anal. Calcd for C₂₉H₃₆N₄O₃·HCl·2.2H₂O: C, 61.68; H, 7.39; N, 9.92. Found: C, 61.60; H, 7.33; N, 9.89.

Example 25

2,3-Dihydro-1'-{3-[2-(S)-(2-methanesulfonamidoethyl)aminocarbonylindolin-1-yl]-3-oxopropyl}spiro[1H-indene-1,4'-piperidine] hydrochloride

A mixture of 2,3-dihydro-1'-{3-[2-(S)-(2-aminoethyl)aminocarbonylindolin-1-yl]-3-oxopropyl}spiro[1H-indene-1,4'-piperidine] (this was prepared in Example 23, 55.2 mg, 0.052 mmol), mesyl chloride (6 μl, 0.077 mmol), and triethylamine (21.6 μl, 0.155 mmol) in CH₂Cl₂ (2 ml) was stirred at room temperature for 1 day. The reaction mixture was diluted with saturated NaHCO₃ aqueous solution and extracted with CH₂Cl₂. The extracts combined were dried (Na₂SO₄), filtered, and concentrated. The residue was purified by preparative TLC (CH₂Cl₂/MeOH:10/1) to give 10.5 mg (38.7 %) of free base as amorphous solid.

This compound showed broadened spectra in proton NMR except for the following peaks.

¹H NMR (270 MHz, CDCl₃) δ 7.06 (1H, dd, J = 7.3, 7.8 Hz), 2.90 (3H, s), 2.03 (2H, t, J = 7.4 Hz), 1.75-1.50 (2H, m).

This was converted to HCl salt similar to that described in Example 1 to give 10.5 mg of HCl salt as a white solid.

¹H NMR (300 MHz, CDCl₃) δ 10.22 (1H, br.s), 8.15 (1H, d, J = 7.2 Hz), 7.90-7.00 (10H, m), 5.30-5.05 (1H, m), 4.30-2.85 (17H, m, including 3H, s, at 2.96 ppm), 2.75-
5 2.45 (2H, m), 2.40-1.90 (3H, m), 1.85-1.65 (2H, m).

MS (ESI positive) m/z: 525 (M+H)⁺.

IR(KBr): 3400, 2936, 2700, 2573, 1655, 1483, 1313, 1151, 758 cm⁻¹.

Preparation 12

Methyl 2-(benzothiazol-2-one-1-yl)-4-hydroxybutyrate

10 To a stirred solution of 2-hydroxybenzothiazole (300 mg, 1.98 mmol) in DMF (5 ml) was added NaH (60 % oil suspension, 160 mg, 3.97 mmol) at room temperature. To this mixture was added α-bromo-γ-butyrolactone (660 mg, 3.97 mmol) and resulting reaction mixture was stirred at room temperature for 1 h, and at 60 °C for 30 minutes. Then NaH (80 mg, 1.98 mmol) and α-bromo-γ-butyrolactone (330 mg, 1.98 mmol)
15 was added to the reaction mixture and stirred at 60 °C for 1 h. The reaction mixture was poured into aqueous NaHCO₃ solution and extracted with ethyl acetate. The extracts combined were dried (MgSO₄) and concentrated. The residue was purified by silica gel column chromatography (hexane / ethyl acetate : 3 / 2) to give 0.35 g (75 %) of lactone derivative as white solid.

20 ¹H NMR (300 MHz, CDCl₃) δ 7.47 (1H, dd, J = 0.9, 7.6 Hz), 7.32 (1H, ddd, J = 1.3, 7.5, 7.7 Hz), 7.20 (1H, ddd, J = 1.1, 7.7, 7.7 Hz), 6.93 (1H, d, J = 8.0 Hz), 5.45-5.30 (1H, m), 4.71 (1H, ddd, J = 2.4, 9.2, 9.3 Hz), 4.46 (1H, ddd, J = 7.0, 9.3, 10.1 Hz), 2.88-2.62 (2H, m).

To a stirred suspension of the above lactone derivative (0.39 g, 1.66 mmol) in MeOH
25 (12 ml) was added c-H₂SO₄ (1 ml) and the reaction mixture was stirred at 60 °C for 2 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extracts combined were washed with aqueous NaHCO₃ solution and brine, dried (MgSO₄), filtered, and concentrated. The residue was purified by silica gel column chromatography (CH₂Cl₂/MeOH: 10/1) followed by preparative TLC (1 mm thick
30 plate, CH₂Cl₂/MeOH: 20/1) to give 173 mg (39 %) of the title compound as a colorless oil.

¹H NMR (270 MHz, CDCl₃) δ 7.48 (1H, dd, J = 1.3, 7.7 Hz), 7.30 (1H, ddd, J = 1.5, 7.7, 7.9 Hz), 7.19 (1H, ddd, J = 1.1, 7.6, 7.7 Hz), 7.00 (1H, d, J = 7.9 Hz), 5.47 (1H, dd, J = 4.6, 10.7 Hz), 3.80-3.74 (1H, m), 3.74 (3H, s), 3.50-3.40 (1H, m), 2.67-2.53 (1H, m), 2.35-2.22 (1H, m), 2.06-1.97 (1H, m).

5

Preparation 13

2,3-Dihydro-1'-[3-(benzothiazol-2-one-1-yl)-3-methoxycarbonylpropyl]spiro[1H-indene-1,4'-piperidine]

To a stirred solution of methyl 2-(benzothiazol-2-one-1-yl)-4-hydroxybutyrate (0.21 g, 0.79 mmol) and triethylamine (0.14 ml, 1.03 mmol) in CH₂Cl₂ (5 ml) was added
10 mesyl chloride (67 μl, 0.86 mmol) at 0 °C. After 15 min stirring, the reaction mixture was poured into aqueous NaHCO₃ solution and extracted with CH₂Cl₂. The extracts combined were dried (MgSO₄), filtered, and concentrated. To this residue was added toluene and concentrated again to give 0.30 g of crude mesylate as colorless oil.

¹H NMR (270 MHz, CDCl₃) δ 7.47 (1H, br.d, J = 7.7 Hz), 7.35-7.15 (2H, m), 7.19
15 (1H, br.d, J = 8.2 Hz), 5.37-5.27 (1H, m), 4.45-4.35 (1H, m), 4.17-4.07 (1H, m), 3.75 (3H, s), 2.94 (3H, s), 2.90-2.78 (1H, m), 2.65-2.50 (1H, m).

A mixture of this oil (0.30 g, 0.79 mmol), 2,3-dihydrospiro[1H-indene-1,4'-piperidine] hydrochloride (0.194 g, 0.87 mmol), and diisopropylethylamine (0.31 g, 2.37 mmol) in MeOH (10 ml) was stirred at 60 °C for 14 h and at 80 °C for 4 h. The reaction mixture
20 was concentrated, then diluted with CH₂Cl₂, washed with aqueous NaHCO₃ solution, dried (MgSO₄), filtered, and concentrated. The residue was purified by silica gel column chromatography (CH₂Cl₂/MeOH: 30/1) to give 165 mg (48%) of title compound as colorless oil.

¹H NMR (270 MHz, CDCl₃) δ 7.45 (1H, dd, J = 1.6, 8.2 Hz), 7.33-7.26 (1H, m), 7.22-
25 7.12 (6H, m), 5.47-5.36 (1H, m), 3.74 (3H, s), 2.90-2.82 (3H, m, including 2H, t, J = 7.1 Hz at 2.86 ppm), 2.65-2.50 (2H, m), 2.42-2.25 (3H, m), 2.15-2.05 (2H, m), 1.95 (2H, t, J = 7.3 Hz), 1.92-1.65 (2H, m), 1.60-1.37 (2H, m).

Example 26

2,3-Dihydro-1'-[3-(benzothiazol-2-one-1-yl)-3-hydroxymethylpropyl]spiro[1H-indene-1,4'-piperidine] hydrochloride

30

To a stirred solution of 2,3-dihydro-1'-[3-(benzothiazol-2-one-1-yl)-3-

methoxycarbonyl-propyl]spiro[1*H*-indene-1,4'-piperidine] (40 mg, 0.092 mmol) in THF (2 ml) was added LiAlH₄ (3.5 mg, 0.092 mmol) at 0 °C. After 30 min stirring, LiAlH₄ (7 mg, 0.184 mmol) was added to the reaction mixture and stirring was continued another 10 min at 0 °C. The reaction mixture was quenched with 15 µl of water, 15 µl of 2N NaOH solution, and 45 µl of water, then the resulting mixture was stirred for 20 min at room temperature. After Celite filtration, the filtrate was concentrated. The residue was purified by preparative TLC (CH₂Cl₂/MeOH: 10/1, then ethyl acetate) to give 8 mg (22 %) of free form of title compound as white solid. ¹H NMR (270 MHz, CDCl₃) δ 7.44-7.40 (1H, m), 7.34-7.30 (2H, m), 7.24-7.12 (6H, m), 4.65-4.40 (1H, m), 4.20 (1H, dd, J = 6.4, 11.7 Hz), 3.95 (1H, dd, J = 7.6, 11.8 Hz), 3.16-3.02 (1H, m), 2.90 (2H, t, J = 7.2 Hz), 2.85-2.75 (1H, m), 2.62-2.48 (3H, m), 2.39-2.26 (1H, m), 2.20-2.08 (1H, m), 2.08-1.84 (5H, m, including 2H, t, J = 7.4 Hz at 2.00 ppm), 1.65-1.50 (2H, m).

This was treated with HCl solution in MeOH followed by concentration to give 8 mg of HCl salt as white amorphous solid.

MS (ESI positive) m/z: 409 (M+H)⁺.

Preparation 14

2,3-Dihydro-1'-[3-(benzothiazol-2-one-1-yl)-3-carboxypropyl]spiro[1*H*-indene-1,4'-piperidine]

A mixture of 2,3-dihydro-1'-[3-(benzothiazol-2-one-1-yl)-3-methoxycarbonylpropyl]spiro[1*H*-indene-1,4'-piperidine] (110 mg, 0.25 mmol) and 2N NaOH solution (0.5 ml, 1 mmol) in THF (2 ml) and MeOH (1 ml) was stirred at room temperature for 16 h. The reaction mixture was diluted with ethyl acetate, washed with HCl solution and brine, dried (MgSO₄), filtered, and concentrated to give 103 mg (96 %) of title compound as white solid.

¹H NMR (300 MHz, DMSO-*d*₆) δ 7.73 (1H, d, J = 7.9 Hz), 7.46-7.36 (2H, m), 7.30-7.05 (5H, m), 5.45-5.35 (1H, m), 3.55-2.95 (9H, m), 2.86 (2H, t, J = 7.1 Hz), 2.80-2.63 (1H, m), 2.25-1.95 (4H, m, including 2H, t, J = 7.5 Hz at 2.02 ppm), 1.70-1.56 (2H, m). MS(EI direct) m/z : 422(M)⁺.

Example 27

2,3-Dihydro-1'-[3-(benzothiazol-2-one-1-yl)-3-(*N,N*-dimethylaminocarbonyl)propyl]spiro[1*H*-indene-1,4'-piperidine] hydrochloride

This was prepared according to the procedure described in Example 11 using 2,3-dihydro-1'-[3-(benzothiazol-2-one-1-yl)-3-carboxypropyl]spiro[1*H*-indene-1,4'-piperidine] instead of 2,3-dihydro-1'-[3-(2-carboxyindolin-1-yl)-3-oxopropyl]spiro[1*H*-indene-1,4'-piperidine]. Yield was 30 mg (71 %). Product was
5 colorless amorphous solid.

¹H NMR (270 MHz, CDCl₃) δ 7.55-7.49 (1H, m), 7.46-7.41 (1H, m), 7.30-7.09 (6H, m), 5.72-5.62 (1H, m), 2.96 (3H, s), 2.95 (3H, s), 2.88-2.73 (4H, m, including 2H, t, J = 7.2 Hz at 2.85 ppm), 2.50-2.22 (4H, m), 2.20-1.80 (5H, m, including 2H, t, J = 7.4 Hz at 1.93 ppm), 1.70-1.55 (1H, m), 1.50-1.35 (2H, m).

10 This was treated with HCl solution in MeOH followed by concentration to give 30 mg of HCl salt as white amorphous solid.

MS (ESI positive) m/z: 450 (M+H)⁺.

IR(KBr): 3439, 2932, 2563, 1655, 1589, 1472, 758 cm⁻¹

Anal. Calcd for C₂₆H₃₁N₃O₂S-HCl-H₂O: C, 61.95; H, 6.80; N, 8.34. Found: C,
15 62.33; H, 7.00; N, 7.89.

Example 28

2,3-Dihydro-1'-[3-(benzothiazol-2-one-1-yl)-3-(2-*N,N*-dimethylaminoethylaminocarbonyl)propyl]spiro[1*H*-indene-1,4'-piperidine] hydrochloride

20 This was prepared according to the procedure described in Example 27 using *N,N*-dimethylethylenediamine instead of dimethylamine hydrochloride. Yield was 30 mg (80 %). Product was colorless oil.

¹H NMR (270 MHz, CDCl₃) δ 7.45 (1H, br.d, J = 7.7 Hz), 7.32-7.10 (7H, m), 6.77 (1H, br.s), 5.41 (1H, dd, J = 5.3, 9.0 Hz), 3.40-3.20 (2H, m), 2.90-2.75 (3H, m,
25 including 2H, t, J = 7.4 Hz at 2.85 ppm), 2.70-2.50 (2H, m), 2.45-1.75 (16H, m, including 6H, s at 2.05 ppm and 2H, t, J = 7.2 Hz at 1.93 ppm), 1.70-1.30 (3H, m).

This was treated with HCl solution in MeOH followed by concentration to give 32 mg of HCl salt as white amorphous solid.

MS (ESI positive) m/z: 493 (M+H)⁺.

30 IR(KBr): 3408, 2934, 2691, 1670, 1537, 1472, 758 cm⁻¹

Anal. Calcd for C₂₈H₃₆N₄O₂S-2HCl-1.2H₂O: C, 57.27; H, 6.93; N, 9.54. Found:

C, 57.623; H, 7.31; N, 9.07.

Example 29

2,3-Dihydro-1'-[3-(3-ethylbenzimidazol-2-one-1-yl)propyl]spiro[1*H*-indene-1,4'-piperidine] hydrochloride

5 NaH (60 % oil suspension, 11.7 mg, 0.293 mmol) was washed with hexane (2 ml x 2) and decanted, then DMF (1 ml) was added. To a stirred this suspension was added a solution of 2,3-dihydro-1'-[3-(benzimidazol-2-one-1-yl)propyl]spiro[1*H*-indene-1,4'-piperidine] (66.1 mg, 0.193 mmol) in DMF (1.5 ml) at room temperature. After stirring for 0.5 h, a solution of iodoethane (57.1 mg, 0.366 mmol) was dropwisely added to the
10 reaction mixture at 0 °C and the resulting mixture was stirred at room temperature for 19 h. The reaction mixture was diluted with saturated aqueous NaHCO₃ solution and extracted with ethyl acetate. The extracts combined were washed with water, dried (Na₂SO₄), filtered, and concentrated to give 67.5 mg of crude product, which was purified by preparative TLC (CH₂Cl₂/MeOH: 15/1) to give 30.5 mg (43 %) of free
15 form of title compound as pale yellow oil.

¹H NMR (270 MHz, CDCl₃) δ 7.25-6.98 (8H, m), 4.01-3.91 (4H, m), 2.92-2.82 (4H, m), 2.46 (2H, t, J = 6.9 Hz), 2.20-2.07 (2H, m), 2.06-1.76 (6H, m), 1.58-1.48 (2H, m), 1.35 (3H, t, J = 7.2 Hz).

This was converted to citric acid salt according to the procedure described in Example
20 34 to give 38.3 mg of citrate as white amorphous solid.

MS (ESI positive) m/z: 390 (M+H)⁺.

IR(KBr): 3416, 2937, 2584, 1686, 1492, 1420, 1192, 756 cm⁻¹

Anal. Calcd for C₂₅H₃₁N₃O-C₆H₈O₇-1.2H₂O: C, 61.72; H, 6.92; N, 6.97. Found: C, 61.83; H, 6.94; N, 6.51.

25

Example 30

2,3-Dihydro-1'-[3-(2-acetamidobenzimidazol-1-yl)propyl]spiro[1*H*-indene-1,4'-piperidine] citrate

To a stirred solution of 2,3-Dihydro-1'-[3-(2-aminoanilino)propyl]spiro[1*H*-indene-1,4'-piperidine] (this was prepared in the first step of Example 18, 105.7 mg, 0.315
30 mmol) in THF (1 ml) was added a solution of cyanogen bromide (33.4 mg, 0.315 mmol) in mixed solvent of THF (1 ml) and water (1 ml) at room temperature. After

16.5 h, the reaction mixture was basified by 25 % NH₃ solution in water at °C and extracted with CH₂Cl₂. The extracts combined were dried (Na₂SO₄), filtered, and concentrated to give 114.3 mg of crude product. To a solution of this compound (53.1 mg, 0.147 mmol) in CH₂Cl₂ (1.5 ml) was added catalytic amount of 4-
5 dimethylaminopyridine, triethylamine (41 µl, 0.726 mmol), and a solution of acetyl chloride (17.3 mg, 0.221 mmol) in CH₂Cl₂ (1.5 ml) at 0 °C. After 2 h stirring, the reaction mixture was warmed to room temperature and stirred another 3 h. The reaction mixture was quenched with saturated aqueous NaHCO₃ solution (10 ml) and extracted with CH₂Cl₂. The extracts combined were washed with brine, dried
10 (Na₂SO₄), filtered, and concentrated. The residue was purified by preparative TLC (CH₂Cl₂/MeOH: 15/1) to afford 7.6 mg (13 %) of free form of title compound as pale yellow oil.

¹H NMR (270 MHz, CDCl₃) δ 7.35-7.10 (8H, m), 4.25-4.15 (4H, m), 2.96-2.82 (8H, m), 2.22-1.96 (7H, m, including 3H, s, at 2.17 ppm), 1.75-1.50 (3H, m).

15 MS (EI direct) m/z: 402 (M⁺), 227, 189.

This was converted to citric acid salt according to the procedure described in Example 34 to give 4.6 mg of citrate as white amorphous solid.

Anal. Calcd for C₂₅H₃₀N₄O-C₆H₈O₇-1.5H₂O: C, 59.89; H, 6.65; N, 9.01. Found: C, 60.15; H, 6.58; N, 8.76.

20

Example 31

2,3-Dihydro-1'-{3-[3-(2-hydroxyethyl)benzimidazol-2-one-1-yl]propyl}spiro[1*H*-indene-1,4'-piperidine] citrate

This was prepared according to the procedure described in Example 29 using *t*-butyldimethylsilyloxyethyl bromide instead of iodoethane followed by deprotection
25 using tetrabutylammonium fluoride in THF. Yield was 48.4 mg (57 %). Product was colorless oil.

¹H NMR (270 MHz, CDCl₃) δ 7.23-6.99 (8H, m), 4.09-3.92 (6H, m), 2.92-2.80 (4H, m, including 2H, t, J = 7.2 Hz), 2.45 (2H, t, J = 7.1 Hz), 2.19-2.07 (2H, m), 2.05-1.83 (6H, m), 1.75 (1H, br.s), 1.58-1.46 (2H, m).

30 MS (EI direct) m/z: 405 (M⁺), 375, 275, 200.

This was converted to citric acid salt according to the procedure described in Example

34 to give 11.6 mg of citrate as white amorphous solid.

IR(KBr): 3406, 2939, 2579, 1686, 1495, 1416, 1192, 756 cm⁻¹

Anal. Calcd for C₂₅H₃₁N₃O₂-C₆H₈O₇-2H₂O: C, 58.76; H, 6.84; N, 6.63. Found: C, 58.93; H, 6.62; N, 6.33.

5

Example 32

2,3-Dihydro-1'-{3-[3-(2-aminoethyl)benzimidazol-2-one-1-yl]propyl}spiro[1*H*-indene-1,4'-piperidine] citrate

This was prepared according to the procedure described in Example 29 using *N*-(2-bromoethyl)phthalimide instead of iodoethane followed by deprotection using
10 hydrazine hydrate in MeOH. Yield was 20.1 mg (10.8 %). Product was colorless oil.

¹H NMR (270 MHz, CDCl₃) δ 7.23-7.02 (8H, m), 4.02-3.92 (4H, m), 3.08 (2H, t, J = 6.2 Hz), 2.92-2.80 (4H, m, including 2H, t, J = 7.4 Hz at 2.88 ppm), 2.46 (2H, t, J = 6.9 Hz), 2.20-2.07 (2H, m), 2.06-1.83 (6H, m), 1.58-1.48 (2H, m), 1.26 (2H, br.s),.

MS (EI direct) m/z: 404 (M⁺), 277, 200.

15 This was converted to citric acid salt according to the procedure described in Example 34 to give 7.5 mg of citrate as white amorphous solid.

Anal. Calcd for C₂₅H₃₂N₄O-C₆H₈O₇-3H₂O: C, 57.22; H, 7.13; N, 8.61. Found: C, 57.35; H, 6.82; N, 8.45.

Example 33

2,3-Dihydro-1'-{3-[3-(2-acetamidoethyl)benzimidazol-2-one-1-yl]propyl}spiro[1*H*-indene-1,4'-piperidine] citrate

To a stirred solution of 2,3-dihydro-1'-{3-[3-(2-aminoethyl)benzimidazol-2-one-1-yl]propyl}spiro[1*H*-indene-1,4'-piperidine] (12.7 mg, 0.031 mmol, this was prepared in Example 32) in CH₂Cl₂ (1.5 ml) was added catalytic amount of 4-
25 dimethylaminopyridine and triethylamine (7.9 μl, 0.056 mmol) followed by addition of acetyl chloride (2.6 μl, 0.037 mmol) at 0 °C. After 1 h stirring at 0 °C and 2 h stirring at room temperature, acetyl chloride (2.6 μl, 0.037 mmol) and triethylamine (7.9 μl, 0.056 mmol) were added to the reaction mixture at 0 °C. After 1 h stirring at 0 °C and 2 h stirring at room temperature, the reaction mixture was quenched with
30 saturated aqueous NaHCO₃ solution and extracted with CH₂Cl₂. The extracts combined were washed with brine, dried (Na₂SO₄), and concentrated to give 14 mg

of crude product, which was purified by preparative TLC (CH₂Cl₂/MeOH: 10/1) to afford 12.5 mg (90 %) of free form of title compound as colorless oil.

¹H NMR (270 MHz, CDCl₃) δ 7.24-7.02 (8H, m), 6.40 (1H, br.s), 4.07 (2H, t, J = 5.6 Hz), 3.98 (2H, t, J = 6.9 Hz), 3.64-3.55 (2H, m), 2.92-2.80 (4H, m, including 2H, t, J = 7.3 Hz at 2.89 ppm), 2.46 (2H, t, J = 6.8 Hz), 2.20-2.07 (2H, m), 2.05-1.83 (9H, m, including 3H, s, at 1.95 ppm), 1.60-1.46 (2H, m).

This was converted to citric acid salt according to the procedure described in Example 34 to give 8.7 mg of citrate as white amorphous solid.

MS (ESI positive) m/z: 447 (M+H)⁺.

10 IR(KBr): 3400, 2943, 2579, 1690, 1495, 1418, 1198, 754 cm⁻¹

Anal. Calcd for C₂₇H₃₄N₄O₂·C₆H₈O₇·1.9H₂O: C, 58.90; H, 6.86; N, 8.33.
Found: C, 59.22; H, 6.57; N, 7.93

Example 34

2,3-Dihydro-1'-[3-(2-(S)-N-methylaminocarbonylindolin-1-yl)-3-oxopropyl]spiro[1H-indene-1,4'-piperidine] citrate

This was prepared according to the procedure described in Example 17 using N-methylamine hydrochloride instead of N,N-dimethylethylenediamine. Yield was 32 mg (62 %). Product was colorless amorphous solid.

This compound showed broadened spectra in proton NMR except for the following peaks.

¹H NMR (270 MHz, CDCl₃) δ 2.79 (3H, d, J = 4.8 Hz), 2.35-2.20 (2H, m), 2.05-1.85 (4H, m), 1.62-1.50 (2H, m).

This was dissolved in mixed solvent of CH₂Cl₂ (1 ml) and MeOH (1 ml) followed by addition of citric acid (15 mg, 0.0766 mmol) and resulting mixture was stirred for 2 h.

25 After concentration, the residue was solidified by adding CH₂Cl₂-hexane. The resulting solid was collected by filtration and washed with ether to give 37 mg of citrate as white amorphous solid.

MS (ESI positive) m/z: 418 (M+H)⁺.

IR(KBr): 3362, 2937, 2586, 1728, 1653, 1597, 1483, 1411, 758 cm⁻¹

30 Anal. Calcd for C₂₆H₃₁N₃O₂·C₆H₈O₇·2.3H₂O: C, 59.03; H, 6.75; N, 6.45. Found: C, 59.41; H, 6.49; N, 5.87

Example 35**2,3-Dihydro-1'-[3-(2-(S)-*N,N*-dimethylaminocarbonylindolin-1-yl)-3-oxopropyl]spiro[1*H*-indene-1,4'-piperidine] citrate**

This was prepared according to the procedure described in Example 17 using *N,N*-dimethylamine hydrochloride instead of *N,N*-dimethylethylenediamine. Yield was 24 mg (45 %). Product was colorless amorphous solid.

¹H NMR (270 MHz, CDCl₃) δ 8.30 (0.4H, br.d, J = 8.2 Hz), 7.32-7.08 (6.6H, m), 7.03-6.96 (1H, m), 5.54-5.42 (0.6H, m), 5.33-5.21 (0.4H, m), 3.77-3.60 (0.4H, m), 3.55-3.38 (0.6H, m), 3.03-2.80 (14H, m, including 1.2H, s, at 3.00 ppm, 1.8H, s, at 2.98 ppm, 1.2H, s, at 2.93 ppm, and 1.8H, s, at 2.90 ppm), 2.70-2.20 (3H, m), 2.10-1.90 (4H, m), 1.65-1.50 (2H, m).

This was converted to citric acid salt according to the procedure described in Example 34 to give 30 mg of citrate as white amorphous solid.

MS (ESI positive) m/z: 432 (M+H)⁺.

IR(KBr): 3416, 2936, 2561, 1728, 1655, 1597, 1485, 1406, 758 cm⁻¹

Anal. Calcd for C₂₇H₃₃N₃O₂·C₆H₈O₇·H₂O: C, 61.77; H, 6.75; N, 6.55. Found: C, 61.96; H, 6.84; N, 6.24

Example 36**2,3-Dihydro-1'-[3-[2-(S)-(4-morpholinecarbonyl)indolin-1-yl]-3-oxopropyl]spiro[1*H*-indene-1,4'-piperidine] citrate**

This was prepared according to the procedure described in Example 17 using morpholine instead of *N,N*-dimethylethylenediamine. Yield was 37 mg (63 %).

Product was colorless amorphous solid.

¹H NMR (270 MHz, CDCl₃) δ 8.29 (0.4H, br.d, J = 8.0 Hz), 7.35-6.96 (7.6H, m), 5.50-5.30 (1H, m), 3.90-3.40 (10H, m), 3.20-2.70 (8H, m), 2.65-2.20 (3H, m), 2.20-1.90 (4H, m), 1.68-1.50 (2H, m).

This was converted to citric acid salt according to the procedure described in Example 34 to give 45 mg of the title product as white amorphous solid.

MS (ESI positive) m/z: 474 (M+H)⁺.

IR(KBr): 3414, 2930, 2573, 1728, 1655, 1597, 1485, 1437, 1236, 1115, 758 cm⁻¹

Anal. Calcd for C₂₉H₃₅N₃O₃·C₆H₈O₇·1.5H₂O: C, 60.68; H, 6.69; N, 6.07. Found:

C, 60.62; H, 6.66; N, 5.71

Preparation 15

2,3-Dihydro-1'-[3-[(2R)-2-(aminocarbonyl)-2,3-dihydro-1*H*-indol-1-yl]-3-oxopropyl] spiro[1*H*-indene-1,4'-piperidine] and 2,3-Dihydro-1'-[3-[(2S)-2-(aminocarbonyl)-2,3-dihydro-1*H*-indol-1-yl]-3-oxopropyl]spiro[1*H*-indene-1,4'-piperidine]

Racemic 2,3-Dihydro-1'-[3-[2-(aminocarbonyl)-2,3-dihydro-1*H*-indol-1-yl]-3-oxopropyl] spiro[1*H*-indene-1,4'-piperidine] (60mg, 0.15 mmol, this was prepared in Example 13) was separated by preparative HPLC on chiral stationary phase (DAICEL CHIRALPAK AS, 20x250 mm, hexane/EtOH/Et₂NH:50/50/0.1 as eluent, 6 ml/min.). Former fraction was (R)-enantiomer, obtained with e.e.>99% (HPLC).

Later fraction was (S)-enantiomer, obtained with e.e.>99% (HPLC).

(S)-Enantiomer was also prepared according to the procedure described in Example 14 using (2S)-indolinecarboxamide instead of methyl (2S)-indolinecarboxylate. Yield was 82 mg (59 %). Product was pale brown amorphous solid.

(S)-Enantiomer showed broadened spectra in proton NMR except for the following peaks.

¹H NMR (270 MHz, CDCl₃) δ 2.40-2.20 (2H, m), 2.10-1.85 (4H, m), 1.75-1.50 (2H, m).

MS (ESI positive) m/z: 404 (M+H)⁺.

Example 37

2,3-Dihydro-1'-[3-[(2R)-2-(aminocarbonyl)-2,3-dihydro-1*H*-indol-1-yl]-3-oxopropyl] spiro[1*H*-indene-1,4'-piperidine] citrate

2,3-Dihydro-1'-[3-[(2R)-2-(aminocarbonyl)-2,3-dihydro-1*H*-indol-1-yl]-3-oxopropyl] spiro[1*H*-indene-1,4'-piperidine] (20mg) was converted to citric acid salt according to the procedure described in Example 34 to give 28 mg of the title product as white amorphous solid.

MS (ESI positive) m/z: 404 (M+H)⁺.

Example 38

2,3-Dihydro-1'-[3-[(2S)-2-(aminocarbonyl)-2,3-dihydro-1*H*-indol-1-yl]-3-oxopropyl] spiro[1*H*-indene-1,4'-piperidine] citrate

2,3-Dihydro-1'-[3-[(2S)-2-(aminocarbonyl)-2,3-dihydro-1*H*-indol-1-yl]-3-oxopropyl]

spiro[1*H*-indene-1,4'-piperidine] (27mg) was converted to citric acid salt according to the procedure described in Example 34 to give 33 mg of the title product as white amorphous solid.

MS (ESI positive) m/z: 404 (M+H)⁺

5

Example 39

2,3-Dihydro-1'-[3-(2-hydroxymethylindolin-1-yl)propyl]spiro[1*H*-indene-1,4'-piperidine] citrate

To a stirred solution of 2,3-Dihydro-1'-[3-(2-hydroxymethylindolin-1-yl)-3-oxopropyl]spiro[1*H*-indene-1,4'-piperidine] (0.13 g, 0.34 mmol, this was prepared in Example 19) in THF (5ml) was added LiAlH₄ (40mg, 1.05 mmol) at 0°C. The resulting reaction mixture was stirred at the same temperature for 2.5 h., quenched by the following addition with water (50μl), 2N NaOH (50μl), and water (150μl), and stirred for 30 min. The resulting mixture was filtered through a pad of celite, and the filtrate was concentrated *in vacuo*. The residue was purified by preparative TLC (1 mm thick silica gel plate: CH₂Cl₂/MeOH:10/1) to afford 8.8 mg (7 %) of free base as a pale yellow amorphous.

¹H NMR (300 MHz, CDCl₃) δ 7.35-7.00 (6H, m), 6.66 (1H, t, J = 7.3Hz), 6.49 (1H, d, J = 7.3 Hz), 3.95-3.70 (3H, m), 3.57-3.45 (1H, m), 3.27-3.15 (1H, m), 3.13-2.85 (6H, m), 2.78-2.65 (1H, m), 2.43-2.22 (2H, m), 2.20-1.82 (8H, m), 1.65-1.48 (2H, m).

This was converted to citric acid salt according to the procedure described in Example 34 to give 10 mg of the title product as a white amorphous solid.

MS (ESI positive) m/z: 377 (M+H)⁺.

Example 40

2,3-Dihydro-1'-[3-(3,4-dihydro-1(2*H*)-quinolinyl)-3-oxopropyl]spiro[1*H*-indene-1,4'-piperidine] hydrochloride

This was prepared according to the procedure described in Example 1 using 1,2,3,4-tetrahydroquinoline instead of methyl indoline-2-carboxylate. 14 mg (36 %) of free form of title compound was obtained as colorless oil.

¹H NMR (300 MHz, CDCl₃) δ 7.24-7.08 (8H, m), 3.81 (2H, t, J = 6.6Hz), 2.87 (2H, t, J = 7.5Hz), 2.84-2.72 (6H, m), 2.73 (2H, t, J = 6.6Hz), 2.24-2.12 (2H, m), 2.03-1.82 (6H, m), 1.56-1.46 (2H, m).

This was converted to HCl salt similar to that described in Example 1 to afford 10 mg

of the title product as white amorphous solid.

MS (ESI positive) m/z : 375 ($M+H$)⁺.

IR(KBr): 3422, 2937, 2559, 1655, 1490, 1398, 1203, 750 cm^{-1}

Example 41

5 **2,3-Dihydro-1'-[3-[2-(aminocarbonyl)-2,3-dihydro-4*H*-1,4-benzothiazin-4-yl]-3-oxopropyl]spiro[1*H*-indene-1,4'-piperidine] citrate**

This was prepared according to the procedure described in Example 1 using 3,4-dihydro-2*H*-1,4-benzothiazine-2-carboxamide (this was prepared according to known procedure: Butler Richard C.M. *et al*, *J. Heterocycl. Chem.* **1985**, 22, 177) instead of
10 methyl indoline-2-carboxylate. 3 mg (4 %) of free form of title compound was obtained as pale brown oil.

This compound showed broadened spectra in proton NMR.

This was converted to citric acid salt according to the procedure described in Example 34 to give 3 mg of the title product as a white solid.

15 MS (ESI positive) m/z : 436 ($M+H$)⁺.

Preparation 16

2,3-Dihydro-1'-[3-[(2*S*)-2-[[[(3*R*)-1-benzyl-3-pyrrolidiny]amino]carbonyl]-2,3-dihydro-1*H*-indol-1-yl]-3-oxopropyl]spiro[1*H*-indene-1,4'-piperidine]

This was prepared according to the procedure described in Example 17 using (3*R*)-1-benzyl-3-aminopyrrolidine instead of *N,N*-dimethylethylenediamine. 490 mg (88 %) of
20 title product was obtained as a pale yellow solid.

This compound showed broadened spectra in proton NMR.

MS (ESI positive) m/z : 563 ($M+H$)⁺.

Example 42

25 **2,3-Dihydro-1'-[3-[(2*S*)-2-[[[(3*R*)-1*H*-3-pyrrolidiny]amino]carbonyl]-2,3-dihydro-1*H*-indol-1-yl]-3-oxopropyl]spiro[1*H*-indene-1,4'-piperidine] citrate**

A mixture of 2,3-dihydro-1'-[3-[(2*S*)-2-[[[(3*R*)-1-benzyl-3-pyrrolidiny]amino]carbonyl]-2,3-dihydro-1*H*-indol-1-yl]-3-oxopropyl]spiro[1*H*-indene-1,4'-piperidine] (490 mg, 0.87 mmol), 2*N* HCl (2 ml), and 10% Pd-C (100 mg)
30 in MeOH (10 ml) was stirred at room temperature under hydrogen atmosphere (4 atm) for 8 h. The reaction mixture was filtered through a pad of celite and the filtrate was concentrated *in vacuo*. The resulting residue was purified by preparative TLC (1 mm

thick silica gel plate: CH₂Cl₂/MeOH/ 25%NH₃:100/10/1) to afford 296 mg (72 %) of free base as a pale yellow amorphous..

¹H NMR (270 MHz, CDCl₃) δ 8.35-8.23 (0.3H, m), 7.40-6.70 (7.7H, m), 5.25-4.85 (1H, m), 4.40-4.20 (1H, m), 3.70-2.50 (16H, m), 2.35-1.85 (5H, m), 2.00 (2H, t, J = 7.3Hz), 1.75-1.45 (3H, m).

This product (99mg) was converted to citric acid salt according to the procedure described in Example 34 to give 137 mg of the title product as a white amorphous solid.

MS (ESI positive) m/z: 473 (M+H)⁺.

IR(KBr): 3416, 3022, 2941, 1717, 1668, 1597, 1483, 1416, 1269, 758 cm⁻¹

Example 43

2,3-Dihydro-1'-[3-[(2S)-2-[[[(3R)-1-methyl-3-pyrrolidiny]amino]carbonyl]-2,3-dihydro-1*H*-indol-1-yl]-3-oxopropyl]spiro[1*H*-indene-1,4'-piperidine] citrate

To a stirred solution of 2,3-dihydro-1'-[3-[(2S)-2-[[[(3R)-1*H*-3-pyrrolidiny]amino]carbonyl]-2,3-dihydro-1*H*-indol-1-yl]-3-oxopropyl]spiro[1*H*-indene-1,4'-piperidine] (90 mg, 0.19 mmol, this was prepared in Example 42), 37% HCHO (77 μl, 0.95 mmol), and AcOH (33 μl, 0.57 mmol) in MeOH (4 ml) was added NaBH₃CN (24 mg, 0.38 mmol) at room temperature. The resulting reaction mixture was stirred at room temperature for 16 h, then concentrated. The residue was quenched with aqueous NaHCO₃ solution and extracted with CH₂Cl₂. The extracts combined were dried (MgSO₄) and concentrated. The resulting residue was purified by preparative TLC (1 mm thick silica gel plate: CH₂Cl₂/MeOH/25%NH₃:100/10/1) to afford 65 mg (71 %) of free base as a colorless amorphous.

This compound showed broadened spectra in proton NMR.

This was converted to citric acid salt according to the procedure described in Example 34 to give 91 mg of the title product as a white amorphous solid.

MS (ESI positive) m/z: 487 (M+H)⁺.

IR(KBr): 3390, 2934, 1715, 1653, 1595, 1417, 1269, 760 cm⁻¹

Anal. Calcd for C₃₀H₃₈N₄O₂-C₆H₈O₇-3.4H₂O: C, 58.43; H, 7.19; N, 7.57. Found: C, 58.76; H, 7.05; N, 7.17.

Preparation 17

2,3-Dihydro-1'-[3-[(2S)-2-[[[(3S)-1-benzyl-3-pyrrolidinyl)amino]carbonyl]-2,3-dihydro-1*H*-indol-1-yl]-3-oxopropyl]spiro[1*H*-indene-1,4'-piperidine]

This was prepared according to the procedure described in Example 17 using (3S)-1-benzyl-3-aminopyrrolidine instead of *N,N*-dimethylethylenediamine. 375 mg (91 %) of the title product was obtained as a pale yellow amorphous.

This compound showed broadened spectra in proton NMR.

MS (ESI positive) *m/z*: 563 (M+H)⁺.

Example 44

2,3-Dihydro-1'-[3-[(2S)-2-[[[(3S)-1*H*-3-pyrrolidinyl)amino]carbonyl]-2,3-dihydro-1*H*-indol-1-yl]-3-oxopropyl]spiro[1*H*-indene-1,4'-piperidine] citrate

This was prepared according to the procedure described in Example 42 using 2,3-dihydro-1'-[3-[(2S)-2-[[[(3S)-1-benzyl-3-pyrrolidinyl)amino]carbonyl]-2,3-dihydro-1*H*-indol-1-yl]-3-oxopropyl]spiro[1*H*-indene-1,4'-piperidine] instead of 2,3-dihydro-1'-[3-[(2S)-2-[[[(3R)-1-benzyl-3-pyrrolidinyl)amino]carbonyl]-2,3-dihydro-1*H*-indol-1-yl]-3-oxopropyl]spiro[1*H*-indene-1,4'-piperidine]. 253 mg (82 %) of free form of title compound was obtained as a pale yellow amorphous.

¹H NMR (270 MHz, CDCl₃) δ 8.35-8.10 (0.3H, m), 7.40-6.60 (7.7H, m), 5.25-4.80 (1H, m), 4.45-4.25 (1H, m), 3.70-2.50 (16H, m), 2.35-2.20 (2H, m), 2.15-1.85 (3H, m), 2.01 (2H, t, *J* = 7.3Hz), 1.65-1.40 (3H, m).

This product (75mg) was converted to citric acid salt according to the procedure described in Example 34 to give 105 mg of the title product as a white amorphous solid.

MS (ESI positive) *m/z*: 473 (M+H)⁺.

IR(KBr): 3416, 3020, 2939, 1719, 1663, 1578, 1483, 1414, 1269, 758 cm⁻¹

Example 45

2,3-Dihydro-1'-[3-[(2S)-2-[[[(3S)-1-methyl-3-pyrrolidinyl)amino]carbonyl]-2,3-dihydro-1*H*-indol-1-yl]-3-oxopropyl]spiro[1*H*-indene-1,4'-piperidine] citrate

This was prepared according to the procedure described in Example 43 using 2,3-dihydro-1'-[3-[(2S)-2-[[[(3S)-1*H*-3-pyrrolidinyl)amino]carbonyl]-2,3-dihydro-1*H*-indol-1-yl]-3-oxopropyl]spiro[1*H*-indene-1,4'-piperidine] (this was prepared described in Example 44) instead of 2,3-dihydro-1'-[3-[(2S)-2-[[[(3R)-1*H*-3-

pyrrolidinyl)amino]carbonyl]-2,3-dihydro-1*H*-indol-1-yl]-3-oxopropyl]spiro[1*H*-indene-1,4'-piperidine]. 81 mg (75 %) of free form of title compound was obtained as a colorless amorphous.

¹H NMR (270 MHz, CDCl₃) δ 8.35-8.10 (0.3H, m), 7.30-6.40 (7.7H, m), 5.25-4.85 (1H, m), 4.50-4.33 (1H, m), 3.75-2.45 (13H, m), 2.40-2.10 (4H, m), 2.31 (3H, s), 2.08-1.85 (3H, m), 2.01 (2H, t, J = 7.2Hz), 1.65-1.40 (3H, m).

This was converted to citric acid salt according to the procedure described in Example 34 to give 108 mg of the title product as a white amorphous solid.

MS (ESI positive) m/z: 487 (M+H)⁺.

IR(KBr): 3422, 3042, 2939, 1719, 1663, 1597, 1483, 1414, 1269, 760 cm⁻¹

Anal. Calcd for C₃₀H₃₈N₄O₂·C₆H₈O₇·2.8H₂O: C, 59.30; H, 7.13; N, 7.68. Found: C, 59.55; H, 7.05; N, 7.23.

Example 46

2,3-Dihydro-1'-[3-[(2*S*)-2-[(ethylamino)carbonyl]-2,3-dihydro-1*H*-indol-1-yl]-3-oxopropyl]spiro[1*H*-indene-1,4'-piperidine] citrate

This was prepared according to the procedure described in Example 17 using ethylamine instead of *N,N*-dimethylethylenediamine. 136 mg (98 %) of free form of title compound was obtained as colorless amorphous.

¹H NMR (270MHz, DMSO-*d*₆) δ 8.38-8.28 (1H, m), 8.15-8.05 (1H, m), 7.24-7.10 (6H, m), 7.03-6.94 (1H, m), 5.05-4.95 (1H, m), 3.64-3.46 (1H, m), 3.20-2.60 (8H, m), 2.84 (2H, t, J = 7.4Hz), 2.45-2.05 (3H, m), 1.95 (2H, t, J = 7.4Hz), 1.88-1.75 (2H, m), 1.55-1.40 (2H, m), 1.04 (3H, t, J = 7.3Hz).

This was converted to citric acid salt according to the procedure described in Example 34 to give 186 mg of the title product as a white amorphous solid.

MS (ESI positive) m/z: 432 (M+H)⁺.

Anal. Calcd for C₂₇H₃₃N₃O₂·C₆H₈O₇·1.5H₂O: C, 60.91; H, 6.82; N, 6.46. Found: C, 61.10; H, 6.80; N, 6.09.

Example 47

2,3-Dihydro-1'-[3-[(2*S*)-2-[(cyclopropylamino)carbonyl]-2,3-dihydro-1*H*-indol-1-yl]-3-oxopropyl]spiro[1*H*-indene-1,4'-piperidine] citrate

This was prepared according to the procedure described in Example 17 using

cyclopropylamine instead of *N,N*-dimethylethylenediamine. 109 mg (83 %) of free form of title compound was obtained as colorless amorphous.

¹H NMR (300MHz, DMSO-*d*₆) δ 8.46-8.39 (1H, m), 8.09 (1H, d, J = 7.9Hz), 7.22-7.08 (6H, m), 7.02-6.94 (1H, m), 4.99-4.89 (1H, m), 3.61-3.46 (1H, m), 3.03-2.55 (7H, m), 2.84 (2H, t, J = 7.3Hz), 2.40-2.05 (3H, m), 1.96 (2H, t, J = 7.3Hz), 1.85-1.70 (2H, m), 1.50-1.38 (2H, m), 0.70-0.60 (2H, m), 0.48-0.40 (2H, m).

This was converted to citric acid salt according to the procedure described in Example 34 to give 132 mg of the title product as a white amorphous solid.

MS (ESI positive) m/z: 444 (M+H)⁺.

Anal. Calcd for C₂₈H₃₃N₃O₂·C₆H₈O₇·2H₂O: C, 60.79; H, 6.75; N, 6.26. Found: C, 60.96; H, 6.51; N, 6.87.

Example 48

2,3-Dihydro-1'-[3-[(2S)-2-(1-piperidinylcarbonyl)-2,3-dihydro-1*H*-indol-1-yl]-3-oxopropyl]spiro[1*H*-indene-1,4'-piperidine] citrate

This was prepared according to the procedure described in Example 17 using piperidine instead of *N,N*-dimethylethylenediamine. 112 mg (80 %) of free form of title compound was obtained as pale yellow amorphous.

¹H NMR (270MHz, DMSO-*d*₆) δ 8.11 (1H, d, J = 8.1Hz), 7.25-7.10 (6H, m), 7.05-6.94 (1H, m), 5.70-5.60 (1H, m), 3.76-3.18 (5H, m), 3.05-2.50 (6H, m), 2.84 (2H, t, J = 7.4Hz), 2.35-2.10 (3H, m), 1.95 (2H, t, J = 7.4Hz), 1.88-1.35 (10H, m).

This was converted to citric acid salt according to the procedure described in Example 34 to give 145 mg of the title product as a white amorphous solid.

MS (ESI positive) m/z: 472 (M+H)⁺.

Anal. Calcd for C₃₀H₃₇N₃O₂·C₆H₈O₇·2.3H₂O: C, 61.32; H, 7.09; N, 5.96. Found: C, 61.39; H, 6.59; N, 5.56.

Example 49

2,3-Dihydro-1'-[3-[(2S)-2-[[*N*-[2-(dimethylamino)ethyl]-*N*-methylamino]carbonyl]-2,3-dihydro-1*H*-indol-1-yl]-3-oxopropyl]spiro[1*H*-indene-1,4'-piperidine] citrate

This was prepared according to the procedure described in Example 17 using *N,N,N'*-trimethylethylenediamine instead of *N,N*-dimethylethylenediamine. 96 mg (80 %) of free form of title compound was obtained as a pale yellow amorphous.

This compound showed broadened spectra in proton NMR.

This product (68mg) was converted to citric acid salt according to the procedure described in Example 34 to give 90 mg of the title product as a white amorphous solid.

MS (ESI positive) m/z: 489 (M+H)⁺.

- 5 Anal. Calcd for C₃₀H₄₀N₄O₂·C₆H₈O₇·2.5H₂O: C, 59.57; H, 7.36; N, 7.72. Found: C, 59.83; H, 7.27; N, 7.17.

Example 50

2,3-Dihydro-1'-[3-oxo-3-(3-oxo-3,4-dihydro-1(2*H*)-quinoxaliny)propyl]spiro[1*H*-indene-1,4'-piperidine] citrate

- 10 This was prepared according to the procedure described in Example 1 using 3,4-dihydro-1*H*-quinoxalin-2-one (this was prepared according to known procedure: TenBrink Ruth E. *et al*, *J. Med. Chem.* **1994**, *37*, 758) instead of methyl indoline-2-carboxylate. 23 mg (13 %) of free form of title compound was obtained as pale brown oil.

- 15 ¹H NMR (300 MHz, CDCl₃) δ 9.06 (1H, s), 7.26-7.07 (7H, m), 7.01-6.96 (1H, m), 4.52 (2H, s), 2.87 (2H, t, J = 7.3Hz), 2.86-2.74 (6H, m), 2.26-2.12 (2H, m), 1.97 (2H, t, J = 7.3Hz), 1.96-1.80 (2H, m), 1.56-1.46 (2H, m).

This was converted to citric acid salt according to the procedure described in Example 34 to give 29 mg of the title product as a pale brown solid.

- 20 MS (ESI positive) m/z: 390 (M+H)⁺.

IR(KBr): 3402, 2930, 1693, 1601, 1504, 1394, 1198, 760 cm⁻¹

Anal. Calcd for C₂₄H₂₇N₃O₂·C₆H₈O₇·0.4CH₂Cl₂·2H₂O: C, 56.03; H, 6.16; N, 6.45. Found: C, 55.87; H, 5.81; N, 6.08.

Preparation 18

- 25 **1-Acryloyl-1'-benzyloxycarbonylspiro[indoline-3,4'-piperidine]**

- To a stirred solution of acryloyl chloride (0.24 g, 2.61 mmol) in CH₂Cl₂ (5 ml) was added a mixture of 1'-benzyloxycarbonylspiro[indoline-3,4'-piperidine] (0.70 g, 2.17 mmol, this was prepared according to known procedure: Maligres Peter E. *et al*, *Tetrahedron* **1997**, *53*, 10983) and triethylamine (0.60 ml, 4.34 mmol) in CH₂Cl₂ (4ml) at 0°C. The resulting reaction mixture was stirred at the same temperature for 20 min., quenched with aqueous NaHCO₃ solution and extracted with CH₂Cl₂. The extracts combined were washed with *d*-HCl, dried (MgSO₄), filtered, and concentrated.
- 30

The resulting residue was purified by silica gel column chromatography (hexane/AcOEt: 1/1 as an eluent) to afford 0.47 g (58 %) of title compound as pale yellow amorphous.

¹H NMR (270 MHz, CDCl₃) δ 8.40-8.25 (1H, m), 7.40-6.95 (8H, m), 6.70-6.40 (2H, m), 5.82-5.73 (1H, m), 5.15 (2H, s), 4.28-4.10 (2H, m), 3.99 (2H, s), 3.03-2.82 (2H, m), 1.87-1.70 (2H, m), 1.68-1.53 (2H, m).

Preparation 19

2,3-Dihydro-1'-[3-[1'-benzyloxycarbonylspiro[indoline-3,4'-piperidine]-1-yl]-3-oxopropyl]spiro[1*H*-indene-1,4'-piperidine]

A mixture of 1-acryloyl-1'-benzyloxycarbonylspiro[indoline-3,4'-piperidine] (0.47 g, 1.3 mmol), 2,3-dihydrospiro[1*H*-indene-1,4'-piperidine] hydrochloride (0.31 g, 1.4 mmol), and triethylamine (0.23 ml, 1.6 mmol) in THF (8 ml) was stirred at 60 °C for 16 h. Then the reaction mixture was quenched with NaHCO₃ solution, and extracted with CH₂Cl₂. The extracts combined were dried (MgSO₄), filtered, and concentrated. The residue was purified by silica gel column chromatography (CH₂Cl₂/MeOH: 40/1 as eluent) to give 0.57 g (72 %) of title compound as colorless amorphous.

¹H NMR (270MHz, CDCl₃) δ 8.24 (1H, d, J = 8.1Hz), 7.45-7.02 (12H, m), 5.18 (2H, s), 4.34-4.18 (2H, m), 3.96 (2H, s), 3.10-2.70 (8H, m), 2.91 (2H, t, J = 7.3Hz), 2.38-2.22 (2H, m), 2.03 (2H, t, J = 7.3Hz), 2.00-1.53 (8H, m).

Example 51

2,3-Dihydro-1'-[3-[spiro[indoline-3,4'-piperidine]-1-yl]-3-oxopropyl]spiro[1*H*-indene-1,4'-piperidine] citrate

A mixture of 2,3-Dihydro-1'-[3-[1'-benzyloxycarbonylspiro[indoline-3,4'-piperidine]-1-yl]-3-oxopropyl]spiro[1*H*-indene-1,4'-piperidine] (0.57 g, 1.00 mmol) and 10% Pd-C (50 mg) in MeOH (8 ml) was stirred at room temperature under hydrogen atmosphere for 14 h. The reaction mixture was filtered through a pad of celite and the filtrate was concentrated *in vacuo* to give crude product (0.42 g, 98 %) as a colorless amorphous. This resulting crude product (90 mg) was purified by preparative TLC (1 mm thick silica gel plate: CH₂Cl₂/MeOH/25%NH₃:100/10/1) to afford 74 mg (81 %) of free base as a colorless amorphous.

¹H NMR (270 MHz, CDCl₃) δ 8.23 (1H, d, J = 7.9Hz), 7.28-7.14 (6H, m), 7.11-7.03 (1H, m), 3.96 (2H, s), 3.20-3.08 (2H, m), 3.02-2.68 (10H, m), 2.38-2.24 (2H, m), 2.08-

1.80 (7H, m), 1.72-1.52 (4H, m).

This was converted to citric acid salt according to the procedure described in Example 34 to give 101 mg of the title product as a white amorphous solid.

MS (ESI positive) m/z : 430 ($M+H$)⁺.

5 IR(KBr): 3412, 2932, 1717, 1653, 1597, 1483, 1420, 1281, 760 cm^{-1}

Anal. Calcd for $\text{C}_{28}\text{H}_{35}\text{N}_3\text{O}-\text{C}_6\text{H}_8\text{O}_7-2\text{H}_2\text{O}$: C, 62.09; H, 7.20; N, 6.39. Found: C, 62.17; H, 7.16; N, 6.09.

Example 52

**2,3-Dihydro-1'-[3-[1'-methylspiro[indoline-3,4'-piperidine]-1-yl]-3-oxopropyl]
10 spiro[1*H*-indene-1,4'-piperidine] citrate**

This was prepared according to the procedure described in Example 43 using 2,3-Dihydro-1'-[3-[spiro[indoline-3,4'-piperidine]-1-yl]-3-oxopropyl]spiro[1*H*-indene-1,4'-piperidine] (this was prepared in Example 52) instead of 2,3-dihydro-1'-[3-[(2*S*)-2-[[[(3*R*)-1*H*-3-pyrrolidinyl)amino]carbonyl]-2,3-dihydro-1*H*-indol-1-yl]-3-oxopropyl]spiro[1*H*-indene-1,4'-piperidine]. 127 mg (97 %) of free form of title
15 compound was obtained as a colorless amorphous.

¹H NMR (270 MHz, CDCl_3) δ 8.22 (1H, d, $J = 8.1\text{Hz}$), 7.28-7.14 (6H, m), 7.10-7.02 (1H, m), 3.90 (2H, s), 3.04-2.70 (10H, m), 2.38-1.90 (10H, m), 2.36 (3H, s), 1.76-1.52 (4H, m).

20 This was converted to citric acid salt according to the procedure described in Example 34 to give 174 mg of the title product as a white amorphous solid.

MS (ESI positive) m/z : 444 ($M+H$)⁺.

IR(KBr): 3412, 2932, 1717, 1655, 1597, 1483, 1420, 1273, 760 cm^{-1}

Anal. Calcd for $\text{C}_{29}\text{H}_{37}\text{N}_3\text{O}-\text{C}_6\text{H}_8\text{O}_7-2.5\text{H}_2\text{O}$: C, 61.75; H, 7.40; N, 6.17. Found:
25 C, 61.86; H, 7.14; N, 5.81.

Example 53

**2,3-Dihydro-1'-[3-[(2*S*)-2-[(4-methyl-1-piperadiny)carbonyl]-2,3-dihydro-1*H*-
indol-1-yl]-3-oxopropyl]spiro[1*H*-indene-1,4'-piperidine] citrate**

A mixture of 2,3-dihydro-1'-[3-(2-(*S*)-carboxyindolin-1-yl)-3-oxopropyl]spiro[1*H*-
30 indene-1,4'-piperidine] (35 mg, 0.088 mmol, this was prepared in Preparation 9), *N*-methylpiperadine (29 μl , 0.263 mmol), WSC (50 mg, 0.263 mmol), HOBt (36 mg,

0.263 mmol), and triethylamine (37 μ l, 0.263 mmol) in CH₂Cl₂ (3 ml) was stirred at room temperature for 18 h. The reaction mixture was diluted with saturated aqueous NaHCO₃ solution and extracted with CH₂Cl₂. The extracts combined were dried (Na₂SO₄), filtered, and concentrated. The residue was purified by NH-silica gel column chromatography (50 g, Hexane/Acetone: 3/1) to give 46 mg (63 %) of free form of title compound as colorless oil.

Two isomers with a ratio of 1:1 were observed in CDCl₃ solution.

¹H NMR (270 MHz, CDCl₃) δ 8.30 (0.5H, d, J = 8.2 Hz), 7.33-7.07 (6H, m), 7.00 (0.5H, t, J = 7.4 Hz), 5.48 (0.5H, d, J = 9.7 Hz), 5.23 (0.5H, d, J = 9.1 Hz), 3.80-3.40 (5H, m), 3.25-2.80 (7H, m, including 2H, t, J = 7.4 Hz at 2.90 ppm), 2.60-2.15 (8H, m), 2.17 (3H, s), 2.07-1.85 (4H, m, including 2H, t, J = 7.4 Hz at 2.02 ppm), 1.56 (2H, d, J = 13.8 Hz).

This was converted to citric acid salt according to the procedure described in Example 34 to give 70 mg of title compound as white amorphous solid.

MS (ESI positive) m/z: 487 (M+H)⁺.

IR(KBr): 3371, 2939, 1720, 1661, 1597, 1483, 1418, 1219, 976, 760 cm⁻¹

Anal. Calcd for C₃₀H₃₈N₄O₂-2C₆H₈O₇-4.5H₂O: C, 52.99; H, 6.67; N, 5.89.

Found: C, 53.00; H, 6.49; N, 6.10.

Example 54

2,3-Dihydro-1'-[3-[(2S)-2-[[[2-(1-pyrrolidiny)ethyl]amino]carbonyl]-2,3-dihydro-1H-indol-1-yl]-3-oxopropyl]spiro[1H-indene-1,4'-piperidine] citrate

This was prepared according to the procedure described in Example 17 using 1-(2-aminoethyl)pyrrolidine instead of N,N-dimethylethylenediamine. 25 mg (41 %) of free form of title compound was obtained as colorless oil.

This compound showed broadened spectra in proton NMR except for the following peaks.

¹H NMR (300 MHz, CDCl₃) δ 2.50-2.25 (2H, m), 2.15-1.95 (4H, m, including 2H, t, J = 7.4 Hz at 2.02 ppm), 1.81 (4H, m), 1.59 (2H, d, J = 13.0 Hz).

This was converted to citric acid salt according to the procedure described in Example 34 to give 32 mg of title compound as white amorphous solid.

MS (ESI positive) m/z: 501 (M+H)⁺.

IR(KBr): 3400, 2939, 1728, 1655, 1597, 1483, 1411, 1215, 760 cm^{-1}

Anal. Calcd for $\text{C}_{31}\text{H}_{40}\text{N}_4\text{O}_2 \cdot 2\text{C}_6\text{H}_8\text{O}_7 \cdot 3\text{H}_2\text{O}$: C, 55.00; H, 6.66; N, 5.97. Found: C, 55.38; H, 6.53; N, 6.20.

Example 55

5 **2,3-Dihydro-1'-[3-[(2*S*)-2-[[[2-(4-morpholinyl)ethyl]amino]carbonyl]-2,3-dihydro-1*H*-indol-1-yl]-3-oxopropyl]spiro[1*H*-indene-1,4'-piperidine] citrate**

This was prepared according to the procedure described in Example 17 using *N*-(2-aminoethyl)morpholine instead of *N,N*-dimethylethylenediamine. 54 mg (85 %) of free form of title compound was obtained as oil.

10 ^1H NMR (270 MHz, CDCl_3) δ 8.24 (1H, m), 7.30-7.13 (6H, m), 7.07 (1H, t, $J = 7.6$ Hz), 6.88 (1H, br.s), 5.03 (1H, m), 3.75-3.40 (6H, m), 3.40-3.15 (4H, m), 3.15-2.83 (8H, m, including 2H, t, $J = 7.4$ Hz at 2.91 ppm), 2.50-2.20 (6H, m), 2.10-1.94 (4H, m, including 2H, t, $J = 7.3$ Hz at 2.02 ppm), 1.58 (2H, d, $J = 13.4$ Hz).

This was converted to citric acid salt according to the procedure described in Example 15 34 to give 80 mg of title compound as white amorphous solid.

MS (ESI positive) m/z : 517 ($\text{M}+\text{H}$) $^+$.

IR(KBr): 3400, 2941, 1732, 1653, 1597, 1483, 1461, 1416, 1211, 758 cm^{-1}

Anal. Calcd for $\text{C}_{31}\text{H}_{40}\text{N}_4\text{O}_3 \cdot 2\text{C}_6\text{H}_8\text{O}_7 \cdot 3\text{H}_2\text{O}$: C, 54.08; H, 6.54; N, 5.87. Found: C, 54.01; H, 6.43; N, 5.74.

20

Example 56

2,3-Dihydro-1'-[3-[(2*S*)-2-[(3-dimethylamino-1-pyrrolidinyl)carbonyl]-2,3-dihydro-1*H*-indol-1-yl]-3-oxopropyl]spiro[1*H*-indene-1,4'-piperidine] citrate

This was prepared according to the procedure described in Example 17 using 3-(Dimethylamino)pyrrolidine instead of *N,N*-dimethylethylenediamine. 56 mg (90 %) 25 of free form of title compound was obtained as red oil. This compound showed broadened spectra in proton NMR.

This was converted to citric acid salt according to the procedure described in Example 34 to give 88 mg of title compound as white amorphous solid.

MS (ESI positive) m/z : 501 ($\text{M}+\text{H}$) $^+$.

30 IR(KBr): 3396, 2941, 2581, 1724, 1655, 1597, 1483, 1411, 1200, 759 cm^{-1}

Anal. Calcd for $\text{C}_{31}\text{H}_{40}\text{N}_4\text{O}_2 \cdot 2\text{C}_6\text{H}_8\text{O}_7 \cdot 3\text{H}_2\text{O}$: C, 55.00; H, 6.66; N, 5.97. Found:

C, 55.43; H, 6.33; N, 5.57.

Example 57

2,3-Dihydro-1'-[3-[(2*S*)-2-[[4-piperidinyl]amino]carbonyl]-2,3-dihydro-1*H*-indol-1-yl]-3-oxopropyl]spiro[1*H*-indene-1,4'-piperidine] citrate

5 A mixture of 2,3-dihydro-1'-[3-(2-(*S*)-carboxyindolin-1-yl)-3-oxopropyl]spiro[1*H*-indene-1,4'-piperidine] (130 mg, 0.321 mmol, this was prepared in Preparation 9), 4-Amino-1-benzyl-piperidine (0.197 ml, 0.964 mmol), WSC (123 mg, 0.643 mmol), HOBt (88 mg, 0.643 mmol), and triethylamine (134 μ l, 0.964 mmol) in CH₂Cl₂ (5 ml) was stirred at room temperature for 2 days. The reaction mixture was diluted with
10 saturated aqueous NaHCO₃ solution and extracted with CH₂Cl₂. The extracts combined were dried (Na₂SO₄), filtered, and concentrated. The residue was purified by NH-silica gel column chromatography (100 g, Hexane/Acetone: 2/1 as eluent) to give 230 mg of amido product as white amorphous solid. This compound was used for the next step without further purification.

15 MS (EI direct) *m/z*: 576 (M)⁺

A suspension mixture of this amido (230 mg), 10 % palladium on activated carbon (100 mg) and MeOH (5 ml) was stirred under hydrogen atmosphere at room temperature for 20 h. After the removal of the catalyst by filtration, the filtrate was concentrated. The resulting crude oil was purified by preparative TLC (1 mm thick
20 plate, CH₂Cl₂/MeOH/Et₃N: 100/10/1) and recrystallization (CH₂Cl₂-Et₂O) to give 98 mg (63 %, 2 steps) as free form of title compound as oil.

This compound showed broadened spectra in proton NMR.

This was converted to citric acid salt according to the procedure described in Example 34 to give 95 mg of title compound as white amorphous solid.

25 MS (ESI positive) *m/z*: 487 (M+H)⁺.

IR(KBr): 3400, 2943, 1655, 1597, 1483, 1420, 1242, 1215, 760 cm⁻¹

Anal. Calcd for C₃₀H₃₈N₄O₂-C₆H₈O₇-3.4H₂O: C, 58.43; H, 7.19; N, 7.57. Found: C, 58.76; H, 7.15; N, 7.16.

Example 58

30 **2,3-Dihydro-1'-[3-[(2*S*)-2-[[1-methyl-4-piperidinyl]amino]carbonyl]-2,3-dihydro-1*H*-indol-1-yl]-3-oxopropyl]spiro[1*H*-indene-1,4'-piperidine] citrate**

A mixture of 2,3-Dihydro-1'-[3-[(2*S*)-2-[[4-piperidinyl]amino]carbonyl]-2,3-dihydro-

1*H*-indol-1-yl]-3-oxopropyl]spiro[1*H*-indene-1,4'-piperidine] (58 mg, 0.119 mmol, this was prepared in Example 57), 37 % formaldehyde solution in water (45 μ l, 0.594 mmol) and CH₃CN (2 ml) was added NaBH₃CN (11 mg, 0.178 mmol) at room temperature, and the resulting mixture was stirred at room temperature for further 20 h.

5 The reaction mixture was diluted with saturated aqueous NaHCO₃ solution and extracted with CH₂Cl₂. The extracts combined were dried (Na₂SO₄), filtered, and concentrated. The residue was purified by preparative TLC (1 mm thick plate, CH₂Cl₂/MeOH/Et₃N: 100/10/1) to give 37 mg (63 %) of free form of title compound as white solid.

10 ¹H NMR (600 MHz, DMSO-*d*₆) δ 8.27 (1H, d, *J* = 7.5 Hz), 8.09 (1H, d, *J* = 8.0 Hz), 7.20-7.10 (6H, m), 6.97 (1H, t, *J* = 7.4 Hz), 4.98 (1H, d, *J* = 10.8 Hz), 3.61-3.48 (2H, m), 2.97 (1H, d, *J* = 15.1 Hz), 2.84 (2H, t, *J* = 7.3 Hz), 2.77 (2H, d, *J* = 5.4 Hz), 2.74-2.53 (5H, m), 2.35-2.24 (1H, m), 2.22-2.09 (5H, m, including 3H, s, at 2.13 ppm), 2.00-1.90 (4H, m, including 2H, d, *J* = 7.2 Hz at 1.94 ppm), 1.78 (2H, t, *J* = 12.1 Hz),
15 1.71 (2H, t, *J* = 11.1 Hz), 1.50-1.40 (4H, m).

¹³C NMR (150 MHz, CDCl₃) δ 29.3, 31.1, 31.4, 32.4, 34.1, 34.4, 36.4, 36.4, 45.7, 45.8, 45.8, 50.3, 50.5, 53.4, 53.8, 53.8, 60.5, 115.9, 122.2, 123.0, 124.3, 124.3, 126.2, 126.4, 127.0, 129.8, 142.6, 143.6, 151.1, 170.3, 170.3.

This was converted to citric acid salt according to the procedure described in Example
20 34 to give 27 mg of title compound as white amorphous solid.

MS (ESI positive) *m/z*: 501 (M+H)⁺.

IR(KBr): 3227, 3047, 2939, 2710, 1664, 1597, 1558, 1483, 1271, 1242, 1215, 760 cm⁻¹

Anal. Calcd for C₃₁H₄₀N₄O₂-C₆H₈O₇-3H₂O: C, 59.50; H, 7.29; N, 7.50. Found: C,
25 59.37; H, 7.29; N, 7.59.

Example 59

2,3-Dihydro-1'-[3-[(2*S*)-2-[(1-pyrrolidiny)carbonyl]-2,3-dihydro-1*H*-indol-1-yl]-3-oxopropyl]spiro[1*H*-indene-1,4'-piperidine] citrate

A mixture of 2,3-dihydro-1'-[3-(2-(*S*)-carboxyindolin-1-yl)-3-oxopropyl]spiro[1*H*-
30 indene-1,4'-piperidine] (70 mg, 0.173 mmol, this was prepared in Preparation 9), pyrrolidine (43 μ l, 0.519 mmol), WSC (66 mg, 0.346 mmol), HOBT (47 mg, 0.346

mmol), and triethylamine (72 μ l, 0.519 mmol) in CH₂Cl₂ (2 ml) was stirred at room temperature for 1 day. The reaction mixture was diluted with saturated aqueous NaHCO₃ solution and extracted with CH₂Cl₂. The extracts combined were dried (Na₂SO₄), filtered, and concentrated. The residue was purified by preparative TLC (1 mm thick plate, CH₂Cl₂/MeOH: 10/1) to give 50 mg (63 %) of free form of title compound as oil.

¹H NMR (270 MHz, DMSO-*d*₆) δ 8.11 (1H, d, *J* = 8.1 Hz), 7.25-7.07 (6H, m), 6.98 (1H, t, *J* = 7.6 Hz), 5.42 (1H, d, *J* = 8.2 Hz), 3.75-3.56 (2H, m), 3.56-3.25 (4H, m), 3.04 (1H, d, *J* = 17.0 Hz), 2.84 (2H, t, *J* = 7.3 Hz), 2.95-2.50 (4H, m), 2.30-2.05 (3H, m), 2.05-1.88 (4H, m, including 2H, t, *J* = 7.1 Hz at 1.94 ppm), 1.88-1.70 (4H, m), 1.42 (2H, d, *J* = 13.5 Hz).

This was converted to citric acid salt according to the procedure described in Example 34 to give 48 mg of title compound as white amorphous solid.

MS (ESI positive) *m/z*: 458 (M+H)⁺.

IR(KBr): 3400, 2953, 2882, 2570, 1732, 1649, 1597, 1485, 1340, 1312, 1191, 758 cm⁻¹

Anal. Calcd for C₂₉H₃₅N₃O₂·C₆H₈O₇·1.5H₂O: C, 62.12; H, 6.85; N, 6.21. Found: C, 62.42; H, 6.72; N, 6.00.

Example 60

2,3-Dihydro-1'-[3-[(2*S*)-2-[(3-hydroxy-1-pyrrolidinyl)carbonyl]-2,3-dihydro-1*H*-indol-1-yl]-3-oxopropyl]spiro[1*H*-indene-1,4'-piperidine] citrate

A mixture of 2,3-dihydro-1'-[3-(2-(*S*)-carboxyindolin-1-yl)-3-oxopropyl]spiro[1*H*-indene-1,4'-piperidine] (100 mg, 0.247 mmol, this was prepared in Preparation 9), DL-3-pyrrolidinol (62 μ l, 0.742 mmol), WSC (95 mg, 0.494 mmol), HOBt (67 mg, 0.494 mmol), and triethylamine (103 μ l, 0.742 mmol) in CH₂Cl₂ (4 ml) was stirred at room temperature for 20 h. The reaction mixture was diluted with saturated aqueous NaHCO₃ solution and extracted with CH₂Cl₂. The extracts combined were dried (Na₂SO₄), filtered, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/*i*PrOH/NH₄OH: 100/20/1) to give 30 mg (25 %) of free form of title compound as colorless oil.

This compound showed broadened spectra in proton NMR.

This was converted to citric acid salt according to the procedure described in Example 34 to give 16 mg of title compound as white amorphous solid.

MS (ESI positive) m/z : 474 ($M+H$)⁺.

IR(KBr): 3408, 2941, 1719, 1638, 1483, 1420, 1312, 1220, 1192, 760 cm^{-1}

5 Anal. Calcd for $\text{C}_{29}\text{H}_{35}\text{N}_3\text{O}_3\cdot\text{C}_6\text{H}_8\text{O}_7\cdot 2.5\text{H}_2\text{O}$: C, 59.14; H, 6.81; N, 5.91. Found: C, 59.28; H, 6.77; N, 5.83.

Preparation 20

N-(tert-butoxycarbonyl)- 2-{[(2-amino-2-oxoethyl)oxy]methyl}-2,3-dihydro-1H-indole

10 To a stirred solution of NaH (27 mg, 0.665 mmol, 60% oil dispersion in mineral oil) and *N*-(tert-butoxycarbonyl)-2-hydroxymethyl-2,3-dihydro-1*H*-indole (138 mg, 0.554 mmol, this was prepared according to known procedure : Fujita, Takeshi *et al*, *Eur. Pat. Appl.* 1995, EP 676398) in DMF(3 ml) was added a solution of 2-bromoacetamide (153 mg, 8.94 mmol) in DMF (2 ml) at 0°C. The reaction mixture was stirred at room
15 temperature for 20 h. Then the reaction mixture was heated to 100°C with stirring for 2 days. The reaction mixture was cooled to room temperature, and quenched with water. The mixture was concentrated, diluted with EtOAc-toluene (1/2), and washed with water (twice) and brine. The organic layer was dried (Na_2SO_4), filtered, and concentrated. The residue was purified by silica gel column chromatography
20 (Hexane/Acetone: 3/1 as eluent) to give 10 mg (6 %) of title compound as colorless oil. ^1H NMR (300 MHz, CDCl_3) δ 7.60 (1H, m), 7.20-7.12 (2H, m), 6.95 (1H, t, $J = 7.3$ Hz), 6.21 (1H, br. s), 5.42 (1H, br. s), 4.63 (1H, m), 3.92 (2H, d, $J = 2.4$ Hz), 3.66 (2H, d, $J = 4.8$ Hz), 3.34 (1H, dd, $J = 10.3$ Hz, 16.3 Hz), 2.93 (1H, d, $J = 16.7$ Hz), 1.58 (9H, s).

25

Preparation 21

2-{[(2-amino-2-oxoethyl)oxy]methyl}-2,3-dihydro-1*H*-indole

A mixture of *N*-(tert-butoxycarbonyl)- 2-{[(2-amino-2-oxoethyl)oxy]methyl}-2,3-dihydro-1*H*-indole (11.6 mg, 0.0379 mmol, this was prepared in Preparation 20) and CH_2Cl_2 (2 ml) was added trifluoroacetic acid (1 ml) at 0°C. The resulting mixture was
30 stirred at room temperature for 1 h. The reaction mixture was concentrated, basified with NaHCO_3 solution, and extracted with CH_2Cl_2 . The extracts combined were dried (Na_2SO_4), filtered, and concentrated. The residue was purified by preparative TLC

(0.5 mm thick plate, Hexane/Acetone: 1/1) to give 7.0 mg (90 %) of title compound as white amorphous solid.

¹H NMR (300 MHz, CDCl₃) δ 7.09 (1H, d, J = 7.3 Hz), 7.04 (1H, t, J = 7.7 Hz), 6.75 (1H, br. s), 6.73 (1H, dt, J = 0.9 Hz, 7.3 Hz), 6.65 (1H, d, J = 8.1 Hz), 5.74 (1H, br. s),
5 4.17-4.06 (1H, m), 4.01 (1H, s), 4.00 (1H, s), 3.65-3.52 (2H, m), 3.17 (1H, dd, J = 9.2 Hz, 15.8 Hz), 2.74 (1H, dd, J = 7.2 Hz, 15.8 Hz), 1.71 (1H, br. s).

Example 61

2,3-Dihydro-1'-[3-[2-((2-amino-2-oxoethyl)oxy)methyl]-2,3-dihydro-1H-indol-1-yl]-3-oxopropyl]spiro[1H-indene-1,4'-piperidine] citrate

10 To a stirred solution of 2-[[2-(2-amino-2-oxoethyl)oxy]methyl]-2,3-dihydro-1H-indole (7.0 mg, 0.0339 mmol, this was prepared in Preparation 21) and triethylamine (14.2 μl, 0.1018 mmol) in CH₂Cl₂ (1 ml) was added 2,3-dihydro-1'-[2-(chloroformyl)ethyl]spiro[1H-indene-1,4'-piperidine] hydrochloride (11.7 mg, 0.0373 mmol, this was prepared in Preparation 3) at 0°C and the resulting reaction mixture
15 was stirred at room temperature for 20 h. The reaction mixture was poured into a saturated aqueous NaHCO₃ solution and extracted with EtOAc. The organic layer was washed with saturated aqueous NaHCO₃ solution and brine, dried (Na₂SO₄), filtered, and concentrated. The residue was purified by preparative TLC (0.5 mm thick plate, CH₂Cl₂/MeOH: 10/1) to give 12.4 mg (82 %) of free form of title compound as white
20 amorphous solid.

This compound showed broadened spectra in proton NMR except for the following peaks.

¹H NMR (300 MHz, CDCl₃) δ 2.35 (2H, m), 2.07-1.92 (4H, m, including 2H, t, J = 7.3 Hz at 2.03 ppm), 1.59 (2H, d, J = 13.2 Hz).

25 This was converted to citric acid salt according to the procedure described in Example 34 to give 16.2 mg of title compound as white amorphous solid.

MS (ESI positive) m/z: 448 (M+H)⁺.

Example 62

2,3-Dihydro-1'-[3-oxo-3-(2,3,4,5-tetrahydro-1H-benzazepin-1-yl)propyl]spiro[1H-indene-1,4'-piperidine] citrate

30 To a stirred solution of 2,3,4,5-tetrahydro-1H-benzazepine (74 mg, 0.501 mmol, this was prepared according to known procedure : B. D. Astill *et al*, *J. Amer. Chem. Soc.*

1955, 77, 4079) and triethylamine (0.21 ml, 1.504 mmol) in CH₂Cl₂ (5 ml) was added 2,3-dihydro-1'-[2-(chloroformyl)ethyl]spiro[1*H*-indene-1,4'-piperidine] hydrochloride (0.173 g, 0.551 mmol, this was prepared in Preparation 3) at 0°C and the resulting reaction mixture was stirred at room temperature for 20 h. The reaction mixture was poured into a saturated aqueous NaHCO₃ solution and extracted with EtOAc. The organic layer was washed with saturated aqueous NaHCO₃ solution and brine, dried (Na₂SO₄), filtered, and concentrated. The residue was purified by silica gel column chromatography (Hexane/Acetone: 3/1-1/1 as eluent) to give 93 mg (48 %) of free form of title compound as colorless oil.

¹H NMR (270 MHz, CDCl₃) δ 7.27-7.10 (8H, m), 4.72 (1H, br. d, J = 14.2 Hz), 2.86 (2H, t, J = 7.3 Hz), 2.80-2.55 (6H, m), 2.52-2.38 (1H, m), 2.28-1.70 (11H, m, including 2H, t, J = 7.3 Hz at 1.95 ppm), 1.55-1.30 (3H, m, including 2H, d, J = 13.4 Hz at 1.47 ppm).

MS (EI direct) m/z: 388 (M)⁺.

This was converted to citric acid salt according to the procedure described in Example 34 to give 78 mg of title compound as white amorphous solid.

MS (ESI positive) m/z: 389 (M+H)⁺.

IR(KBr): 2937, 2567, 1724, 1645, 1443, 1420, 1211, 764 cm⁻¹

Anal. Calcd for C₂₆H₃₂N₂O-C₆H₈O₇-1.5H₂O: C, 63.25; H, 7.13; N, 4.61. Found: C, 63.51; H, 7.07; N, 4.42.

Example 63

2,3-Dihydro-1'-[3-[(2*S*)-2-[(3-amino-1-pyrrolidinyl)carbonyl]-2,3-dihydro-1*H*-indol-1-yl]-3-oxopropyl]spiro[1*H*-indene-1,4'-piperidine] citrate

A mixture of 2,3-dihydro-1'-[3-(2-(*S*)-carboxyindolin-1-yl)-3-oxopropyl]spiro[1*H*-indene-1,4'-piperidine] (0.200 g, 0.494 mmol, this was prepared in Preparation 9), 3-(Boc-amino)pyrrolidine (0.276 g, 1.483 mmol), WSC (0.190 g, 0.989 mmol), HOBt (0.135 g, 0.989 mmol), and triethylamine (0.207 ml, 1.483 mmol) in CH₂Cl₂ (10 ml) was stirred at room temperature for 20 h. The reaction mixture was diluted with saturated aqueous NaHCO₃ solution and extracted with CH₂Cl₂. The extracts combined were dried (Na₂SO₄), filtered, and concentrated. The residue was purified by silica gel column chromatography (50 g, CH₂Cl₂/MeOH: 10/1 as eluent) to give 0.283 g (99 %) of amido product as yellow oil. This compound was used for the next

step without further purification.

A mixture of this amide (0.283 g, 0.494 mmol), and CH₂Cl₂ (4 ml) was added trifluoroacetic acid (2 ml) at 0°C. The resulting mixture was stirred at room temperature for 1 h. The reaction mixture was concentrated, basified with NaHCO₃ solution, and extracted with CH₂Cl₂. The extracts combined were dried (Na₂SO₄), filtered, and concentrated. The residue was purified by NH-silica gel column chromatography (50 g, Hexane/Acetone: 1/1 as eluent) to give 0.170 g (73 %) of free form of title compound as an oil.

This compound showed broadened spectra in proton NMR.

This was converted to citric acid salt according to the procedure described in Example 34 to give 0.154 g of title compound as white amorphous solid.

MS (ESI positive) m/z: 473 (M+H)⁺.

IR(KBr): 3400, 2937, 1649, 1597, 1483, 1404, 1267, 1213, 760 cm⁻¹

Anal. Calcd for C₂₉H₃₆N₄O₂·C₆H₈O₇·2.4H₂O: C, 59.38; H, 6.95; N, 7.91. Found:

C, 59.78; H, 6.89; N, 7.46.

Example 64

2,3-Dihydro-1'-[3-[(2*S*)-2-[(1-azetidiny)carbonyl]-2,3-dihydro-1*H*-indole-1-yl]-3-oxopropyl]spiro[1*H*-indene-1,4'-piperidine] citrate

A mixture of 2,3-dihydro-1'-[3-(2-(*S*)-carboxyindolin-1-yl)-3-oxopropyl]spiro[1*H*-indene-1,4'-piperidine] (120 mg, 0.297 mmol, this was prepared in Preparation 9), azetidine hydrochloride (56 mg 0.593 mmol), WSC (114 mg, 0.593 mmol), HOBt (81 mg, 0.593 mmol), and triethylamine (0.124 ml, 0.890 mmol) in CH₂Cl₂ (5 ml) was stirred at room temperature for 1 day. The reaction mixture was diluted with saturated aqueous NaHCO₃ solution and extracted with CH₂Cl₂. The extracts combined were dried (Na₂SO₄), filtered, and concentrated. The residue was purified by preparative TLC (1 mm thick plate, CH₂Cl₂/MeOH: 10/1) to give 107 mg (81 %) of free form of title compound as oil.

¹H NMR (270 MHz, DMSO-*d*₆) δ 8.09 (1H, d, J = 7.8 Hz), 7.25-7.10 (6H, m), 6.99 (1H, t, J = 7.3 Hz), 5.20 (1H, d, J = 8.7 Hz), 4.35-4.15 (2H, m), 3.92 (2H, m), 3.57 (1H, dd, J = 11.5 Hz, 16.2 Hz), 2.95-2.78 (4H, m, including 2H, t, J = 7.1 Hz at 2.84 ppm), 2.78-2.60 (2H, m), 2.36-2.10 (4H, m), 1.96 (2H, t, J = 7.4 Hz), 1.81 (1H, br. t, J = 12.4 Hz), 1.45 (2H, d, J = 13.0 Hz).

This was converted to citric acid salt according to the procedure described in Example 34 to give 118 mg of title compound as white amorphous solid.

MS (ESI positive) m/z : 444 ($M+H$)⁺.

IR(KBr): 3414, 2943, 2571, 1728, 1653, 1483, 1418, 1217, 760 cm^{-1}

5 Anal. Calcd for $\text{C}_{28}\text{H}_{33}\text{N}_3\text{O}_2\cdot\text{C}_6\text{H}_8\text{O}_7\cdot 1.8\text{H}_2\text{O}$: C, 61.12; H, 6.73; N, 6.29. Found: C, 61.04; H, 6.67; N, 6.08.

Preparation 22

(2S)-1-acryloyl-N,N-dimethyl-2,3-dihydro-1H-indole-2-carboxamide

To a stirred solution of (2S)-N,N-dimethyl-2,3-dihydro-1H-indole-2-carboxamide
10 (11.07 g, 0.0511 mol, this was prepared according to known procedure : Serradeil-le Gal *et al.* *PCT Int. Appl.* **2001**, WO 0164668) and triethylamine (17.81 ml, 0.1278 mol) in CH_2Cl_2 (200 ml) was added Acryloyl chloride (4.98 ml, 0.0613 mol) at 0°C and the resulting reaction mixture was stirred at 0°C for 2 h. The reaction mixture was poured into a saturated aqueous NaHCO_3 solution and extracted with CH_2Cl_2 . The
15 extracts combined were dried (Na_2SO_4), filtered, and concentrated. The residue was purified by silica gel column chromatography (500 g, Hexane/Acetone: 2/1-1/1 as eluent) to give 8.00 g (64 %) of title compound as white solid.

This compound showed broadened spectra in proton NMR.

MS (EI direct) m/z : 244 (M)⁺.

20

Example 65

1'-[3-[(2S)-2-[(dimethylamino)carbonyl]-2,3-dihydro-1H-indol-1-yl]-3-oxopropyl]spiro[1H-indene-1,4'-piperidine] citrate

A mixture of (2S)-1-acryloyl-N,N-dimethyl-2,3-dihydro-1H-indole-2-carboxamide (66 mg 0.271 mmol, this was prepared in Preparation 22), Spiro[1H-indene-1,4'-
25 piperidine] hydrochloride (120 mg, 0.226 mmol), and triethylamine (94 μl , 0.677 mmol) in THF (3 ml) was stirred at 60°C for 1 day. The reaction mixture was cooled to room temperature and evaporated to remove the solvent. The residue was purified silica gel column chromatography (50 g, Hexane/Acetone: 3/2 then $\text{CH}_2\text{Cl}_2/\text{MeOH}$: 10/1 as eluent) to give 90 mg (93 %) of free form of title compound as oil.

30 Two isomers with a ratio of 1:1 were observed in CDCl_3 solution.

^1H NMR (270 MHz, CDCl_3) δ 8.31 (0.5H, d, $J = 7.9$ Hz), 7.42-7.07 (6.5H, m), 7.00 (1H, t, $J = 7.4$ Hz), 6.85 (1H, d, $J = 5.6$ Hz), 6.75 (1H, d, $J = 5.6$ Hz), 5.47 (0.5H, br. d,

$J = 7.6$ Hz), 5.26 (0.5H, br. d, $J = 7.9$ Hz), 3.69 (0.5H, dd, $J = 11.4$ Hz, 15.2 Hz), 3.46 (0.5H, dd, $J = 11.2$ Hz, 16.0 Hz), 3.25-2.90 (12H, m), 2.70-2.36 (3H, m), 2.22 (2H, dt, $J = 3.5$ Hz, 13.0 Hz), 1.38 (2H, d, $J = 13.4$ Hz).

This was converted to citric acid salt according to the procedure described in Example 34 to give 106 mg of title compound as white amorphous solid.

MS (ESI positive) m/z : 430 ($M+H$)⁺.

IR(KBr): 3420, 2937, 2580, 1728, 1651, 1485, 1404, 1269, 1186, 754 cm^{-1}

Anal. Calcd for $\text{C}_{27}\text{H}_{31}\text{N}_3\text{O}_2\cdot\text{C}_6\text{H}_8\text{O}_7\cdot 2\text{H}_2\text{O}$: C, 60.26; H, 6.59; N, 6.39. Found: C, 60.01; H, 6.36; N, 5.99.

10

Example 66

1'-[3-[(2*S*)-2-[(dimethylamino)carbonyl]-2,3-dihydro-1*H*-indol-1-yl]-3-oxopropyl]spiro[isobenzofuran-1(3*H*),4'-piperidin]-3-one citrate

A mixture of (2*S*)-1-acryloyl-*N,N*-dimethyl-2,3-dihydro-1*H*-indole-2-carboxamide (72 mg 0.295 mmol, this was prepared in Preparation 17), Spiro[isobenzofuran-1(3*H*),4'-piperidin]-3-one hydrochloride (50 mg, 0.246 mmol), and triethylamine (51 μl , 0.369 mmol) in THF (3 ml) was stirred at 60°C for 1 day. The reaction mixture was cooled to room temperature and evaporated to remove the solvent. The residue was purified silica gel column chromatography (50 g, Hexane/Acetone: 3/2 then $\text{CH}_2\text{Cl}_2/\text{MeOH}$: 10/1 as eluent) to give 103 mg (94 %) of free form of title compound as oil.

Two isomers with a ratio of 1:1 were observed in CDCl_3 solution.

^1H NMR (270 MHz, CDCl_3) δ 8.31 (0.5H, d, $J = 7.6$ Hz), 7.88 (1H, d, $J = 7.6$ Hz), 7.67 (1H, t, $J = 7.4$ Hz), 7.52 (1H, t, $J = 7.6$ Hz), 7.42 (1H, d, $J = 7.6$ Hz), 7.32-7.07 (2.5H, m), 7.00 (1H, t, $J = 7.1$ Hz), 5.48 (0.5H, br. d, $J = 7.8$ Hz), 5.24 (0.5H, br. d, $J = 11.0$ Hz), 3.71 (0.5H, dd, $J = 11.9$ Hz, 14.7 Hz), 3.48 (0.5H, dd, $J = 10.9$ Hz, 15.8 Hz), 3.25-2.85 (11H, m), 2.66 (2H, br. t, $J = 12.2$ Hz), 2.60-2.38 (1H, m), 2.38-2.15 (3H, m), 1.74 (2H, d, $J = 13.2$ Hz).

This was converted to citric acid salt according to the procedure described in Example 34 to give 120 mg of title compound as white amorphous solid.

MS (ESI positive) m/z : 448 ($M+H$)⁺.

IR(KBr): 3420, 2936, 2571, 1767, 1734, 1653, 1485, 1406, 1200, 1059, 932, 760 cm^{-1}

Anal. Calcd for $\text{C}_{26}\text{H}_{29}\text{N}_3\text{O}_4\cdot\text{C}_6\text{H}_8\text{O}_7\cdot 2.5\text{H}_2\text{O}$: C, 56.13; H, 6.18; N, 6.14. Found:

30

C, 56.14; H, 5.89; N, 5.79.

Example 67

1'-[3-[(2*S*)-2-[(dimethylamino)carbonyl]-2,3-dihydro-1*H*-indol-1-yl]-3-oxopropyl]spiro[benzofuran-3(2*H*),4'-piperidin]-2-one citrate

5 A mixture of (2*S*)-1-acryloyl *N,N*-dimethyl-2,3-dihydro-1*H*-indole-2-carboxamide (72 mg 0.295 mmol, this was prepared in Preparation 17), Spiro[benzofuran-3(2*H*),4'-piperidin]-2-one hydrochloride (50 mg, 0.246 mmol), and triethylamine (51 μ l, 0.369 mmol) in THF (3 ml) was stirred at 60°C for 1 day. The reaction mixture was cooled to room temperature and evaporated to remove the solvent. The residue was purified
10 silica gel column chromatography (50 g, Hexane/Acetone: 3/2 then CH₂Cl₂/MeOH: 10/1 as eluent) to give 22 mg (20 %) of free form of title compound as colorless oil. Two isomers with a ratio of 1:1 were observed in CDCl₃ solution.

¹H NMR (270 MHz, CDCl₃) δ 8.30 (0.5H, d, *J* = 7.9 Hz), 7.40-7.07 (6.5H, m), 7.00 (1H, t, *J* = 7.9 Hz), 5.48 (0.5H, br. d, *J* = 7.4 Hz), 5.31 (0.5H, br. d, *J* = 6.3 Hz), 3.72
15 (0.5H, dd, *J* = 10.9 Hz, 15.7 Hz), 3.47 (0.5H, dd, *J* = 10.9 Hz, 15.8 Hz), 3.25-2.70 (14H, m), 2.63-2.35 (1H, m), 2.10-1.94 (4H, m).

This was converted to citric acid salt according to the procedure described in Example 34 to give 120 mg of title compound as white amorphous solid.

MS (ESI positive) *m/z*: 448 (M+H)⁺.

20 IR(KBr): 3422, 2937, 2588, 1793, 1732, 1653, 1485, 1406, 1230, 1055, 758 cm⁻¹

Anal. Calcd for C₂₆H₂₉N₃O₄·C₆H₈O₇·3H₂O: C, 55.41; H, 6.25; N, 6.06. Found: C, 55.71; H, 5.89; N, 5.56.

Example 68

1'-[3-[(2*S*)-2-[(dimethylamino)carbonyl]-2,3-dihydro-1*H*-indol-1-yl]-3-oxopropyl]spiro[isobenzofuran-1(3*H*),4'-piperidine] citrate

25 A mixture of (2*S*)-1-acryloyl-*N,N*-dimethyl-2,3-dihydro-1*H*-indole-2-carboxamide (77 mg 0.317 mmol, this was prepared in Preparation 17), Spiro[isobenzofuran-1(3*H*),4'-piperidine] hydrochloride (50 mg, 0.264 mmol), and triethylamine (55 μ l, 0.396 mmol) in THF (3 ml) was stirred at 60°C for 1 day. The reaction mixture was cooled to room
30 temperature and evaporated to remove the solvent. The residue was purified silica gel column chromatography (50 g, Hexane/Acetone: 3/2 then CH₂Cl₂/MeOH: 10/1 as

eluent) to give 107 mg (94 %) of free form of title compound as an oil.

Two isomers with a ratio of 1:1 were observed in CDCl₃ solution.

¹H NMR (270 MHz, CDCl₃) δ 8.30 (0.5H, d, J = 8.1 Hz), 7.32-7.07 (6.5H, m), 6.99 (1H, t, J = 7.4 Hz), 5.47 (0.5H, br. d, J = 7.9 Hz), 5.26 (0.5H, br. d, J = 8.7 Hz), 5.07 (2H, s), 3.69 (0.5H, dd, J = 12.8 Hz, 13.8 Hz), 3.45 (0.5H, dd, J = 11.5 Hz, 15.3 Hz), 3.22-2.85 (12H, m), 2.70-2.42 (3H, m), 2.03 (2H, dt, J = 4.3 Hz, 13.2 Hz), 1.79 (2H, d, J = 12.9 Hz).

This was converted to citric acid salt according to the procedure described in Example 34 to give 130 mg of title compound as white amorphous solid.

MS (ESI positive) m/z: 434 (M+H)⁺.

IR(KBr): 3435, 2934, 2573, 1732, 1655, 1485, 1418, 1045, 1020, 758 cm⁻¹

Anal. Calcd for C₂₆H₃₁N₃O₃·C₆H₈O₇·2H₂O: C, 58.09; H, 6.55; N, 6.35. Found: C, 57.85; H, 6.46; N, 6.08.

Example 69

1'-[3-[(2*S*)-2-[(dimethylamino)carbonyl]-2,3-dihydro-1*H*-indol-1-yl]-3-oxopropyl]spiro[benzofuran-3(2*H*),4'-piperidine] citrate

A mixture of (2*S*)-1-acryloyl-*N,N*-dimethyl-2,3-dihydro-1*H*-indole-2-carboxamide (89 mg 0.365 mmol, this was prepared in Preparation 17), Spiro[benzofuran-3(2*H*),4'-piperidine] (62 mg, 0.304 mmol), and triethylamine (85 μl, 0.609 mmol) in THF (3 ml) was stirred at reflux temperature for 20 h. The reaction mixture was cooled to room temperature and evaporated to remove the solvent. The residue was purified silica gel column chromatography (50 g, EtOAc/*i*PrOH/25%NH₄OH: 100/20/1 then CH₂Cl₂/MeOH: 10/1 as eluent) to give 91 mg (69 %) of free form of title compound as oil.

¹H NMR (300 MHz, DMSO-*d*₆) δ 8.11 (1H, d, J = 8.1 Hz), 7.25-7.15 (3H, m), 7.10, 1H, dt, J = 1.5 Hz, 7.9 Hz), 6.97 (1H, t, J = 8.1 Hz), 6.84 (1H, t, J = 7.3 Hz), 6.75 (1H, d, J = 7.9 Hz), 5.61 (1H, dd, J = 2.8 Hz, 11.0 Hz), 4.35 (2H, s), 3.64 (1H, dd, J = 11.2 Hz, 16.7 Hz), 3.12 (3H, s), 3.01 (1H, dd, J = 16.7 Hz), 2.88 (3H, s), 2.88-2.75 (2H, m), 2.75-2.55 (3H, m), 2.21-1.95 (3H, m), 1.84 (2H, br. t, J = 11.7 Hz), 1.61 (2H, d, J = 13.0 Hz).

This was converted to citric acid salt according to the procedure described in Example

34 to give 98 mg of title compound as white amorphous solid.

MS (ESI positive) m/z : 434 ($M+H$)⁺.

IR(KBr): 3422, 2936, 2573, 1719, 1653, 1483, 1406, 974, 756 cm^{-1}

Anal. Calcd for $\text{C}_{26}\text{H}_{31}\text{N}_3\text{O}_3\cdot\text{C}_6\text{H}_8\text{O}_7\cdot 3\text{H}_2\text{O}$: C, 58.89; H, 6.49; N, 6.44. Found: C,
5 58.72; H, 6.37; N, 6.27.

Preparation 23

Spiro[(2-indanone)-1,4'-piperidine]

To a stirred solution of *N-tert*-butoxycarbonylspiro[(2-indanone)-1,4'-piperidine] (198 mg, 0.658 mmol, this was prepared according to known procedure : Toshiyasu
10 Takemoto *et al. Tetrahedron Asymmetry* 1999, 10, 1787) in CH_2Cl_2 (2 ml) was added trifluoroacetic acid (1 ml) at room temperature and the resulting reaction mixture was stirred for 2 h. The reaction mixture was evaporated to remove the solvents, poured into a saturated aqueous NaHCO_3 solution and extracted with CH_2Cl_2 . The extracts combined were dried (Na_2SO_4), filtered, and concentrated to give 88 mg (67 %) of
15 title compound as brown oil.

^1H NMR (300 MHz, CDCl_3) δ 7.40-7.23 (4H, m), 3.58 (2H, s), 3.35-3.20 (2H, m), 3.10-2.95 (2H, m), 2.44 (1H, br. s), 1.85-1.73 (4H, m).

Example 70

1'-[3-[(2*S*)-2-[(dimethylamino)carbonyl]-2,3-dihydro-1*H*-indol-1-yl]-3-oxopropyl]spiro[(2-indanone)-1,4'-piperidine] citrate

20

A mixture of (2*S*)-1-acryloyl-*N,N*-dimethyl-2,3-dihydro-1*H*-indole-2-carboxamide (0.193 g, 0.789 mmol, this was prepared in Preparation 22), 1-[4-Spiro-piperidine]-2-indanone (88 mg, 0.439 mmol, this was prepared in Preparation 23), and triethylamine (0.183 ml, 1.315 mmol) in THF (4 ml) was stirred at reflux temperature for 1 day. The
25 reaction mixture was cooled to room temperature and evaporated to remove the solvent. The residue was purified silica gel column chromatography (50 g, $\text{CH}_2\text{Cl}_2/\text{MeOH}$: 15/1 as eluent) to give 81 mg (41 %) of free form of title compound as oil.

Two isomers with a ratio of 1:1 were observed in CDCl_3 solution.

^1H NMR (270 MHz, CDCl_3) δ 8.31 (0.5H, d, $J = 7.9\text{Hz}$), 7.42-7.07 (6.5H, m), 7.00
30 (1H, t, $J = 7.4\text{ Hz}$), 6.85 (1H, d, $J = 5.6\text{ Hz}$), 6.75 (1H, d, $J = 5.6\text{ Hz}$), 5.47 (0.5H, br. d, $J = 7.6\text{ Hz}$), 5.26 (0.5H, br. d, $J = 7.9\text{ Hz}$), 3.69 (0.5H, dd, $J = 11.4\text{ Hz}, 15.2\text{ Hz}$), 3.46

(0.5H, dd, $J = 11.2$ Hz, 16.0 Hz), 3.25-2.90 (12H, m), 2.70-2.36 (3H, m), 2.22 (2H, dt, $J = 3.5$ Hz, 13.0 Hz), 1.38 (2H, d, $J = 13.4$ Hz).

This compound (25 mg) was converted to citric acid salt according to the procedure described in Example 34 to give 28 mg of title compound as white amorphous solid.

5 MS (ESI positive) m/z : 446 ($M+H$)⁺.

Example 71

1'-[3-[(2*S*)-2-[(dimethylamino)carbonyl]-2,3-dihydro-1*H*-indol-1-yl]-3-oxopropyl]spiro[(2-hydroxy)indane-1,4'-piperidine] citrate

To a stirred solution of 1'-[3-[(2*S*)-2-[(dimethylamino)carbonyl]-2,3-dihydro-1*H*-indol-1-yl]3-oxopropyl]spiro[3-(2-indanone)-1,4'-piperidine] (40 mg, 0.090 mmol, this was prepared in Example 70) in MeOH (1 ml) was added NaBH₄ (4.1 mg, 1.077 mmol) at 0°C, and the resulting mixture was stirred for 2 h. The reaction mixture was quenched with water, diluted with a saturated aqueous NaHCO₃ solution and extracted with CH₂Cl₂. The extracts combined were dried (Na₂SO₄), filtered, and concentrated. The residue was purified by preparative TLC (0.5 mm thick plate, CH₂Cl₂/MeOH/25%NH₄OH: 100/10/1) to give 23 mg (58 %) of free form of title compound as yellow solid. This compound showed broadened spectra in proton NMR except for the following peaks.

¹H NMR (300 MHz, CDCl₃) δ 2.65-2.40 (3H, m), 2.40-2.07 (4H, m), 2.07-1.90 (1H, m), 1.76 (1H, br. t, $J = 10.3$ Hz), 1.55 (1H, d, $J = 14.1$ Hz).

This was converted to citric acid salt according to the procedure described in Example 34 to give 28 mg of title compound as white amorphous solid.

MS (FAB positive) m/z : 448 ($M+H$)⁺.

Preparation 24

***N*-tert-butoxycarbonylspiro[(2-hydroxy-3-methyl)indane-1,4'-piperidine]**

To a stirred suspension of CuI (101 mg, 0.531 mmol) in THF (30 ml) was added slowly MeMgI (15.8 ml, 0.0133 mol, 0.84 mol/l in Et₂O) at -20°C under N₂. After 10 minutes, *N*-tert-butoxycarbonylspiro[((2,3)-epoxy)indan-1,4'-piperidine] (800 mg, 2.65 mmol, this was prepared according to known procedure : Toshiyasu Takemoto *et al. Tetrahedron Asymmetry* 1999, 10, 1787) in THF (10 ml) was added dropwise. The resulting reaction mixture was stirred at -20°C for 2 h. Excess of reagent was destroyed with saturated aqueous NH₄Cl solution, basified with saturated aqueous

NaHCO₃ solution and extracted with EtOAc. The extracts combined were washed with water and brine, dried (Na₂SO₄), filtered, and concentrated. The residue was purified by silica gel column chromatography (200 g, Hexane/EtOAc: 3/1 as eluent) to give 0.372 g (44 %) of title compound as an oil.

5 ¹H NMR (300 MHz, CDCl₃) δ 7.40-7.20 (4H, m), 3.85-3.67 (4H, m), 3.51-3.40 (1H, m), 3.11-3.00 (8H, m), 2.07-1.96 (2H, m), 1.90-1.75 (2H, m), 1.49 (9H, s), 1.40 (3H, d, J = 6.8 Hz).

MS (EI direct) m/z: 317 (M)⁺

Preparation 25

10 ***N-tert-Butoxycarbonylspiro[{(2-(methylthiocarbonothioyl)oxy)-3-methyl}indane-1,4'-piperidine]***

To a stirred solution of *N-tert*-Butoxycarbonyl-spiro[(2-hydroxy-3-methyl)indane-1,4'-piperidine] (0.121 g, 0.382 mmol, this was prepared in Preparation 24) in THF (3 ml) was added imidazole (2.6 mg, 0.0382 mmol) and NaH (31 mg, 0.764 mmol, 60% oil dispersion in mineral oil), and the resulting mixture was stirred at 0°C for 40 minutes. To the mixture was added CS₂ at 0°C, and the mixture was stirred for further stirred at 0°C for 1.5 h. To the mixture was added MeI, and the mixture was stirred at 0°C for 30 minutes. The reaction was quenched with ice-cooled water, and the product was extracted with EtOAc. The organic layer was dried (Na₂SO₄) and concentrated. The residue was purified by preparative TLC (1 mm thick plate, Hexane/EtOAc: 5/1) to give 85 mg (55 %) of title compound as colorless oil.

15 ¹H NMR (300 MHz, CDCl₃) δ 7.30-7.15 (4H, m), 6.10 (1H, d, J = 4.2 Hz), 4.10-3.82 (2H, m), 3.42-3.31 (1H, m), 3.25-3.10 (1H, m), 3.03 (1H, ddd, J = 2.9 Hz, 11.2 Hz, 13.9 Hz), 2.59 (3H, s), 2.10 (1H, d, J = 14.1 Hz), 1.94-1.63 (3H, m), 1.48 (9H, s), 1.43 (3H, d, J = 7.3 Hz).

25 MS (FAB positive) m/z: 408 (M+H)⁺

Preparation 26

N-tert-Butoxycarbonylspiro[(3-methyl)indane-1,4'-piperidine]

A solution of *N-tert*-Butoxycarbonylspiro[{(2-(methylthiocarbonothioyl)oxy)-3-methyl}indane-1,4'-piperidine] (85 mg, 0.210 mmol, this was prepared in Preparation 25), *n*-Bu₃SnH (62 μl, 0.231 mmol), and azobisisobutyronitrile (17 mg, 0.105 mmol) in toluene (3 ml) was heated under reflux for 3 days. After cooling, the reaction

mixture was concentrated to give a residue, which was purified by silica gel column chromatography (50g, Hexane/EtOAc: 10/1 as eluent) to give 51 mg (82 %) of title compound as colorless oil.

¹H NMR (270 MHz, CDCl₃) δ 7.25-7.20 (4H, m), 4.09 (2H, m), 3.23 (1H, ddd, J = 7.1 Hz, 7.4 Hz, 16.2 Hz), 3.05-2.83 (2H, m), 2.50 (1H, dd, J = 7.6 Hz, 12.7 Hz), 2.04 (1H, dt, J = 4.6 Hz, 13.0 Hz), 1.60-1.30 (16H, m, including 9H, s at 1.49 ppm and 3H, d, J = 6.8 Hz at 1.33 ppm), 1.33 (3H, d, J = 6.8 Hz).

Preparation 27

Spiro[(3-methyl)indane-1,4'-piperidine]

To a stirred solution of *N*-*tert*-Butoxycarbonylspiro[(3-methyl)indan-1,4'-piperidine] (51 mg, 0.171 mmol, this was prepared in Preparation 26) in CH₂Cl₂ (2 ml) was added trifluoroacetic acid (1 ml) at 0°C and the resulting reaction mixture was stirred at room temperature for 2 h. The reaction mixture was evaporated to remove the solvents, poured into a saturated aqueous NaHCO₃ solution and extracted with CH₂Cl₂. The extracts combined were dried (Na₂SO₄), filtered, and concentrated to give 34 mg (100 %) of title compound as colorless oil.

¹H NMR (300 MHz, CDCl₃) δ 7.27-7.15 (4H, m), 3.22 (1H, dd, J = 7.2 Hz, 14.5 Hz), 3.15-3.00 (2H, m), 2.95-2.77 (2H, m), 2.54 (1H, dd, J = 7.7 Hz, 12.8 Hz), 2.34 (1H, br s), 2.07 (1H, dt, J = 4.0 Hz, 12.7 Hz), 1.68-1.15 (7H, m, including 3H, d, J = 6.8 Hz at 1.32 ppm).

Example 72

1'-[3-[(2*S*)-2-[(Dimethylamino)carbonyl]-2,3-dihydro-1*H*-indol-1-yl]-3-oxopropyl]spiro[(3-methyl)indane-1,4'-piperidine] citrate

A mixture of (2*S*)-1-acryloyl-*N,N*-dimethyl-2,3-dihydro-1*H*-indole-2-carboxamide (50 mg, 0.205 mmol, this was prepared in Preparation 22), Spiro[(3-methyl)indan-1,4'-piperidine] (34 mg, 0.171 mmol, this was prepared in Preparation 27), and triethylamine (48 µl, 0.341 mmol) in THF (3 ml) was stirred at reflux temperature for 2 days. The reaction mixture was cooled to room temperature and evaporated to remove the solvent. The residue was purified by silica gel column chromatography (50 g, CH₂Cl₂/MeOH: 10/1 as eluent) to give 66 mg (87 %) of free form of title compound as colorless oil.

¹H NMR (300 MHz, DMSO-*d*₆) δ 8.11 (1H, d, J = 7.9 Hz), 7.25-7.13 (6H, m), 6.98 (1H, t, J = 7.9 Hz), 5.62 (1H, br. d, J = 7.9 Hz), 3.64 (1H, dd, J = 11.0 Hz, 16.5 Hz), 3.50-3.23 (2H, m), 3.23-3.08 (4H, m, including 3H, s, at 3.12 ppm), 3.01 (1H, d, J = 16.5 Hz), 2.95-2.55 (7H, m, including 3H, s, at 2.88 ppm), 2.55-2.40 (1H, m), 2.30-2.00 (3H, m), 1.60-1.35 (3H, m), 1.35-1.20 (1H, m), 1.26 (3H, d, J = 7.0 Hz).

This was converted to citric acid salt according to the procedure described in Example 34 to give 76 mg of title compound as white amorphous solid.

MS (ESI positive) m/z: 446 (M+H)⁺.

IR(KBr): 3400, 2932, 2579, 1734, 1647, 1485, 1404, 1217, 1122, 758 cm⁻¹

Anal. Calcd for C₂₈H₃₅N₃O₂·C₆H₈O₇·5H₂O: C, 59.81; H, 7.09; N, 6.15. Found: C, 59.90; H, 6.76; N, 5.79.

Example 73

1-Methyl-1'-[3-[(2*S*)-2-[(dimethylamino)carbonyl]-2,3-dihydro-1*H*-indol-1-yl]-3-oxopropyl]spiro[indoline-3,4'-piperidine] citrate

A mixture of (2*S*)-1-acryloyl-*N,N*-dimethyl-2,3-dihydro-1*H*-indole-2-carboxamide (64 mg, 0.261 mmol, this was prepared in Preparation 22), 1-Methylspiro[indoline-3,4'-piperidine] (39 mg, 0.217 mmol, this was prepared according to known procedure : Simon M. N. Efange *et al. J. Med. Chem.* 1997, 40, 3905), and triethylamine (45 μl, 0.326 mmol) in THF (3 ml) was stirred at reflux temperature for 1 day. The reaction mixture was cooled to room temperature and evaporated to remove the solvent. The residue was purified by silica gel column chromatography (50 g, Hexane/Acetone: 3/2 then CH₂Cl₂/MeOH: 10/1 as eluent) to give 51 mg (53 %) of free form of title compound as brown oil.

Two isomers with a ratio of 1:1 were observed in CDCl₃ solution.

¹H NMR (300 MHz, CDCl₃) δ 8.29 (0.5H, d, J = 8.1 Hz), 7.31-7.15 (2.5H, m), 7.10 (1H, dt, J = 1.1 Hz, 7.5 Hz), 7.05 (1H, m), 7.00 (1H, t, J = 8.3 Hz), 6.69 (1H, t, J = 7.5 Hz), 6.48 (1H, d, J = 7.7 Hz), 5.46 (0.5H, d, J = 7.2 Hz), 5.35-5.20 (0.5H, m), 3.69 (0.5H, dd, J = 11.0 Hz, 14.9 Hz), 3.46 (0.5H, dd, J = 11.2 Hz, 16.3 Hz), 3.25-2.83 (14H, m), 2.76 (3H, s), 2.60-2.43 (1H, m), 2.22 (2H, t, J = 11.7 Hz), 2.05-1.88 (2H, m), 1.75 (2H, d, J = 13.4 Hz).

This was converted to citric acid salt according to the procedure described in Example

34 to give 136 mg of title compound as brown amorphous solid.

MS (ESI positive) m/z: 447 (M+H)⁺.

IR(KBr): 3398, 2932, 2579, 1732, 1655, 1485, 1406, 1273, 1123, 754 cm⁻¹

Anal. Calcd for C₂₇H₃₄N₄O₂·C₆H₈O₇·H₂O: C, 60.35; H, 6.75; N, 8.53. Found: C,
5 60.06; H, 6.84; N, 8.63.

Preparation 28

2,3-Dihydro-1'-(3-chloropropyl)spiro[1*H*-indene-1,4'-piperidine]

To a stirred solution 2,3-Dihydro-1'-(3-hydroxypropyl)spiro[1*H*-indene-1,4'-piperidine] (0.870 g, 3.55 mmol, this was prepared in Preparation 9) in CHCl₃ (30 ml)
10 was added thionyl chloride (0.388 ml, 5.32 mmol) at room temperature and the resulting reaction mixture was refluxed with stirring for 2 h. After cooling, the reaction mixture was poured into a saturated aqueous NaHCO₃ solution and extracted with CH₂Cl₂. The extracts combined were dried (Na₂SO₄), filtered, and concentrated. The residue was purified by silica gel column chromatography (200g, CH₂Cl₂/MeOH:
15 20/1 as eluent) to give 0.540 g (58 %) of title compound as brown solid.

¹H NMR (270 MHz, CDCl₃) δ 7.35-7.28 (1H, m), 7.26-7.17 (3H, m), 3.68 (2H, t, J = 6.1 Hz), 3.36 (2H, d, J = 11.7 Hz), 3.03-2.90 (4H, m), 2.70 (2H, t, J = 12.5 Hz), 2.55-2.30 (4H, m), 2.05 (2H, t, J = 7.3 Hz), 1.72 (2H, d, J = 14.0 Hz).

Example 74

2,3-Dihydro-1'-[3-(3,3-dimethyl-2-oxo-2,3-dihydro-1*H*-indol-1-yl)propyl]spiro[1*H*-indene-1,4'-piperidine] citrate

A mixture of 2,3-Dihydro-1'-(3-chloropropyl)spiro[1*H*-indene-1,4'-piperidine] (70 mg, 0.265 mmol, this was prepared in preparation 28), 1,3-Dihydro-3,3,-dimethyl-2*H*-indol-2-one (51 mg, 0.318 mmol, this was prepared according to known procedure:
25 David W. Robertson *et al*, *J. Med. Chem.* **1986**, 29, 1832), and KF·Al₂O₃ (0.25 g) in CH₃CN (8 ml) was stirred at reflux temperature for 1 day. After cooling, the reaction mixture was filtered over celite, and the filtrate was concentrated. The residue was purified by NH-silica gel column chromatography (50g, Hexane/EtOAc: 9/1) to give 89 mg (87 %) of free form of title compound as colorless oil.

30 ¹H NMR (270 MHz, CDCl₃) δ 7.30-7.10 (6H, m), 7.04 (1H, dt, J = 1.0 Hz, 7.4 Hz), 6.95 (1H, d, J = 7.8 Hz), 3.79 (2H, t, J = 7.1 Hz), 2.92-2.82 4H, m, including 2H, t, J

= 7.3 Hz at 2.88 ppm), 2.44 (2H, t, J = 6.9 Hz), 2.14 (2H, br. t, J = 10.1 Hz), 2.02-1.83 (6H, m, including 2H, t, J = 7.4 Hz at 1.99 ppm), 1.54 (2H, d, J = 12.9 Hz), 1.37 (6H, s).

This was converted to citric acid salt according to the procedure described in Example 34 to give 88 mg of title compound as white amorphous solid.

MS (ESI positive) m/z: 389 (M+H)⁺.

IR(KBr): 3400, 2934, 1709, 1613, 1387, 1366, 1200, 762 cm⁻¹

Anal. Calcd for C₂₆H₃₂N₂O-C₆H₈O₇-2H₂O: C, 62.32; H, 7.19; N, 4.54. Found: C, 62.27; H, 6.73; N, 4.34.

Example 75

2,3-Dihydro-1'-[3-(3,3-dimethyl-2,3-dihydro-1H-indol-1-yl)-3-oxopropyl]spiro[1H-indene-1,4'-piperidine] citrate

To a stirred solution of 3,3-dimethyl-2,3-dihydro-1H-indole (100 mg, 0.679 mmol, this was prepared according to known procedure : Andrew Kucеровy *et al*, *Synth. Commun.*

1992, 22, 729) and triethylamine (0.28 ml, 2.04 mmol) in CH₂Cl₂ (5 ml) was added 2,3-dihydro-1'-[2-(chloroformyl)ethyl]spiro[1H-indene-1,4'-piperidine] hydrochloride (0.235 g, 0.747 mmol, this was prepared in Preparation 3) at 0°C and the resulting reaction mixture was stirred at room temperature for 1 day. The reaction mixture was poured into a saturated aqueous NaHCO₃ solution and extracted with EtOAc. The organic layer was washed with saturated aqueous NaHCO₃ solution and brine, dried (Na₂SO₄), filtered, and concentrated. The residue was purified by NH-silica gel column chromatography (50 g, Hexane/EtOAc: 5/1-3/1 as eluent) to give 0.227 g (86 %) of free form of title compound as oil.

¹H NMR (270 MHz, CDCl₃) δ 8.21 (1H, d, J = 8.1 Hz), 7.25-7.12 (6H, m), 7.06 (1H, t, J = 7.4 Hz), 3.82 (2H, s), 3.00-2.85 (6H, m), 2.70 (2H, t, J = 7.7 Hz), 2.29 (2H, dt, J = 2.5 Hz, 12.4 Hz), 2.08-1.88 (4H, m, including 2H, t, J = 7.4 Hz at 2.03 ppm), 1.59 (2H, d, J = 16.2 Hz), 1.36 (6H, s).

This was converted to citric acid salt according to the procedure described in Example 34 to give 0.267 g of title compound as white amorphous solid.

MS (ESI positive) m/z: 389 (M+H)⁺.

IR(KBr): 2955, 1724, 1665, 1597, 1483, 1421, 1286, 752 cm⁻¹

Anal. Calcd for C₂₆H₃₂N₂O·C₆H₈O₇·0.3H₂O: C, 65.58; H, 6.98; N, 4.78. Found: C, 65.62; H, 7.00; N, 4.85.

Example 76

5 **2,3-Dihydro-1'-[3-(2,3,-dihydro-4*H*-1,4-benzothiazin-4-yl)-3-oxopropyl]spiro[1*H*-indene-1,4'-piperidine] citrate**

To a stirred solution of 2,3-Dihydro-2*H*-1,4-benzothiazine (46 mg, 0.302 mmol, this was prepared according to known procedure : Saverio Florio *et al*, *J. Heterocycl. Chem.* 1982, 19, 237) and triethylamine (0.13 ml, 0.907 mmol) in CH₂Cl₂ (3 ml) was added 2,3-dihydro-1'-[2-(chloroformyl)ethyl]spiro[1*H*-indene-1,4'-piperidine] hydrochloride
10 (95 mg, 0.302 mmol, this was prepared in Preparation 3) at 0°C and the resulting reaction mixture was stirred at room temperature for 1 day. The reaction mixture was poured into a saturated aqueous NaHCO₃ solution and extracted with EtOAc. The organic layer was washed with saturated aqueous NaHCO₃ solution and brine, dried (Na₂SO₄), filtered, and concentrated. The residue was purified by preparative TLC (1
15 mm thick plate, CH₂Cl₂/MeOH/: 10/1) to give 2.9 mg (2.4 %) of free form of title compound as oil.

¹H NMR (270 MHz, CDCl₃) δ 7.30-7.07 (8H, m), 4.00 (2H, m), 3.25 (2H, t, J = 5.77 Hz), 2.87 (2H, t, J = 7.3 Hz), 2.74 (6H, m), 2.17 (2H, br. t, J = 9.6 Hz), 2.05-1.70 (6H, m, including 2H, t, J = 7.4 Hz at 1.96 ppm), 1.49 (2H, d, J = 13.0 Hz).

20 MS (EI direct) m/z: 392 (M)⁺.

This was converted to citric acid salt according to the procedure described in Example 34 to give 5.9 mg of title compound as red amorphous solid.

MS (ESI positive) m/z: 393 (M+H)⁺.

Example 77

25 **2,3-Dihydro-1'-[3-[3-(hydroxymethyl)-2,3,-dihydro-4*H*-1,4-benzoxazin-4-yl]-3-oxopropyl]spiro[1*H*-indene-1,4'-piperidine] citrate**

To a stirred solution of 3,4-Dihydro-2*H*-1,4-benzoxiazin-3-ylmethanol (20 mg, 0.124 mmol, this was prepared according to known procedure : G. W. H. Potter *et al*, *J. Heterocycl. Chem.* 1972, 9, 299) and triethylamine (52 μl, 0.371 mmol) in CH₂Cl₂ (2
30 ml) was added 2,3-dihydro-1'-[2-(chloroformyl)ethyl]spiro[1*H*-indene-1,4'-piperidine] hydrochloride (39 mg, 0.124 mmol, this was prepared in Preparation 3) at 0°C and the resulting reaction mixture was stirred at room temperature for 20 h. The reaction

mixture was poured into a saturated aqueous NaHCO₃ solution and extracted with EtOAc. The organic layer was washed with saturated aqueous NaHCO₃ solution and brine, dried (Na₂SO₄), filtered, and concentrated. The residue was purified by preparative TLC (0.5 mm thick plate, CH₂Cl₂/MeOH: 10/1) to give 7.0 mg (14 %) of free form of title compound as oil.

¹H NMR (270 MHz, CDCl₃) δ 7.24-7.13 (4H, m), 6.78 (2H, t, J = 8.4 Hz), 6.70-6.57 (2H, m), 4.28-4.15 (3H, m), 4.10 (2H, dd, J = 5.3 Hz, 10.7 Hz), 3.80-3.65 (1H, m), 2.97-2.84 (4H, m, including 2H, t, J = 7.3 Hz at 2.89 ppm), 2.84-2.73 (2H, m), 2.61 (2H, t, J = 6.6 Hz), 2.30-2.16 (2H, m), 2.05-1.85 (4H, m, including 2H, t, J = 7.4 Hz at 2.00 ppm), 1.55 (2H, d, J = 13.2 Hz).

This was converted to citric acid salt according to the procedure described in Example 34 to give 9.8 mg of title compound as white amorphous solid.

MS (ESI positive) m/z: 407 (M+H)⁺.

Preparation 29

2,3-Dihydro-1'-[2-(*tert*-butoxycarbonyl)amino-3-ethoxy-3-oxopropyl]spiro[1*H*-indene-1,4'-piperidine]

A mixture of 2,3-Dihydrospiro[1*H*-indene-1,4'-piperidine] hydrochloride (0.352 g, 1.57 mmol, this was prepared according to known procedure : M. S. Chambers *et al*, *J. Med. Chem.* 1992, 35, 2033), Methyl 2-[(*tert*-butoxycarbonyl)amino]acrylate (0.288 g, 1.43 mmol, this was prepared according to known procedure : Paula M. T. Ferreira *et al*, *J. Chem. Soc. Perkin Trans. 1*, 1999, 24, 3697), and triethylamine (0.30 ml, 2.15 mmol) in EtOH (15 ml) was stirred at reflux temperature for 1 day. The reaction mixture was cooled to room temperature and evaporated to remove the solvent. The residue was purified silica gel column chromatography (50 g, Hexane/EtOAc: 9/1-4/1 as eluent) to give 0.172 g (31 %) of title compound as yellow oil.

¹H NMR (300 MHz, CDCl₃) δ 7.23-7.10 (4H, m), 5.40 (1H, m), 4.38-4.10 (3H, m), 2.90-2.65 (6H, m, including 2H, t, J = 7.3 Hz at 2.88 ppm), 2.36-2.22 (2H, m), 1.98 (2H, t, J = 7.4 Hz), 1.89 (2H, dt, J = 3.3 Hz, 12.5 Hz), 1.55-1.45 (11H, m, including 9H, s, at 1.47 ppm), 1.30 (3H, t, J = 7.2 Hz).

Preparation 30

2,3-Dihydro-1'-[3-(indolin-1-yl)-2-(*tert*-butoxycarbonyl)amino-3-oxopropyl]spiro[1*H*-indene-1,4'-piperidine]

A mixture of 2,3-Dihydro-1'-[2-(*tert*-butoxycarbonyl)amino-3-ethoxy-3-oxopropyl]spiro[1*H*-indene-1,4'-piperidine] (0.345 g, 0.889 mmol, this was prepared in Preparation 29), and 2N NaOH (0.67 ml, 1.333 mmol) in THF-MeOH (6 ml-2 ml) was stirred at 60°C for 2 h. The reaction mixture was cooled to room temperature, neutralized by 2N HCl, and evaporated to give crude corresponding carboxylic acid. This was used for the next step without purification.

A mixture of this carboxylic acid, indoline (0.199 ml, 0.178 mmol), WSC (0.341 g, 0.178 mmol), HOBt (0.242 g, 0.178 mmol), and triethylamine (0.372 ml, 0.267 mmol) in CH₂Cl₂ (10 ml) was stirred at room temperature for 3 days. The reaction mixture was diluted with saturated aqueous NaHCO₃ solution and extracted with CH₂Cl₂. The extracts combined were dried (Na₂SO₄), filtered, and concentrated. The residue was purified by silica gel column chromatography (50 g, Hexane/Acetone: 5/1) to give 0.288 g (68 %, 2steps) of title compound as colorless oil.

¹H NMR (270 MHz, CDCl₃) δ 8.24 (1H, d, J = 8.1 Hz), 7.26-7.10 (6H, m), 7.05 (1H, t, J = 7.4 Hz), 5.42 (1H, br.t, J = 7.8 Hz), 4.73 (1H, dt, J = 6.9 Hz, 7.6 Hz), 4.36 (2H, dt, J = 2.5 Hz, 6.8 Hz), 3.25 (2H, t, J = 8.4 Hz), 2.87 (2H, t, J = 7.5 Hz), 3.07-2.65 (4H, m, including 2H, t, J = 6.8 Hz at 2.73 ppm), 2.45-2.20 (2H, m), 2.00-1.75 (4H, m, including 2H, t, J = 7.1 Hz at 1.98 ppm), 1.60-1.35 (11H, m, including 9H, s, at 1.45 ppm).

Example 78

2,3-Dihydro-1'-[2-amino-3-(indolin-1-yl)-3-oxopropyl]spiro[1*H*-indene-1,4'-piperidine] citrate

To a stirred solution of 2,3-Dihydro-1'-[3-(indolin-1-yl)-2-(*tert*-butoxycarbonyl)amino-3-oxopropyl]spiro[1*H*-indane-1,4'-piperidine] (0.288 g, 0.605 mmol, this was prepared in Preparation 30) in CH₂Cl₂ (4 ml) was added trifluoroacetic acid (2 ml) at 0°C and the resulting reaction mixture was stirred at room temperature for 1 h. The reaction mixture was evaporated to remove the solvents, poured into a saturated aqueous NaHCO₃ solution and extracted with CH₂Cl₂. The extracts combined were dried (Na₂SO₄), filtered, and concentrated. The residue was purified by silica gel column chromatography (50 g, CH₂Cl₂/MeOH: 10/1) to give 0.225 g (99 %) of title compound as colorless oil.

¹H NMR (300 MHz, CDCl₃) δ 8.26 (1H, d, J = 8.3 Hz), 7.25-7.13 (6H, m), 7.04 (1H,

dt, $J = 0.9$ Hz, 7.3 Hz), 4.22 (2H, t, $J = 8.3$ Hz), 3.88 (1H, dd, $J = 4.6$ Hz, 8.3 Hz), 3.23 (2H, t, $J = 8.4$ Hz), 3.00 - 2.85 (2H, m), 2.89 (2H, t, $J = 7.5$ Hz), 2.65 (1H, dd, $J = 4.8$ Hz, 12.7 Hz), 2.54 (1H, dd, $J = 8.8$ Hz, 12.8 Hz), 2.42 (1H, br. t, $J = 9.9$ Hz), 2.24 (1H, br. t, $J = 11.4$ Hz), 2.11 (2H, br. s), 2.00 (2H, t, $J = 7.3$ Hz), 2.00 - 1.83 (2H, m), 1.60 - 1.47 (2H, m).

This compound (46 mg) was converted to citric acid salt according to the procedure described in Example 34 to give 56 mg of title compound as white amorphous solid.

MS (ESI positive) m/z : 376 ($M+H$)⁺.

IR(KBr): 3400, 2935, 1719, 1665, 1560, 1485, 1437, 1211, 758 cm^{-1}

Anal. Calcd for $\text{C}_{24}\text{H}_{29}\text{N}_3\text{O}-\text{C}_6\text{H}_8\text{O}_7-1.8\text{H}_2\text{O}$: C, 60.05; H, 6.82; N, 7.00. Found: C, 60.17; H, 6.71; N, 6.66.

Example 79

2,3-Dihydro-1'-[3-(indolin-1-yl)-2-dimethylamino-3-oxopropyl]spiro[1*H*-indene-1,4'-piperidine] citrate

A mixture of 2,3-Dihydro-1'-[2-amino-3-(indolin-1-yl)-3-oxopropyl]spiro[1*H*-indene-1,4'-piperidine] (52 mg, 0.140 mmol, this was prepared in Example 78), 37 % formaldehyde solution in water (51 μl , 0.698 mmol) and CH_3CN (2 ml) was added NaBH_3CN (26 mg, 0.419 mmol) at 0°C , and the resulting mixture was stirred at room temperature for 1 day. The reaction mixture was quenched with water, diluted with saturated aqueous NaHCO_3 solution and extracted with CH_2Cl_2 . The extracts combined were dried (Na_2SO_4), filtered, and concentrated. The residue was purified by preparative TLC (1 mm thick plate, $\text{CH}_2\text{Cl}_2/\text{MeOH}$: 10/1) to give 34 mg (61 %) of free form of title compound as colorless oil.

^1H NMR (270 MHz, CDCl_3) δ 8.30(1H, d, $J = 8.6$ Hz), 7.26-7.10 (6H, m), 7.02 (1H, t, $J = 7.4$ Hz), 4.39 (1H, dd, $J = 9.9$ Hz, 19.0 Hz), 4.19 (1H, dd, $J = 10.1$ Hz, 18.8 Hz), 3.60 (1H, dd, $J = 4.3$ Hz, 7.9 Hz), 3.21 (2H, t, $J = 8.4$ Hz), 3.09 (1H, dd, $J = 4.1$ Hz, 12.7 Hz), 2.97 (1H, br. d, $J = 11.7$ Hz), 2.87 (2H, t, $J = 7.3$ Hz), 2.92-2.78 (1H, m), 2.71 (1H, dd, $J = 3.8$ Hz, 12.7 Hz), 2.42 (6H, s), 2.33 (2H, br. t, $J = 12.0$ Hz), 1.99 (2H, t, $J = 7.4$ Hz), 2.00-1.80 (2H, m), 1.50 (2H, br. t, $J = 13.4$ Hz).

This was converted to citric acid salt according to the procedure described in Example 34 to give 20 mg of title compound as white amorphous solid.

MS (ESI positive) m/z : 404 ($M+H$)⁺.

IR(KBr): 3400, 2941, 2572, 1719, 1655, 1597, 1483, 1420, 1188, 758 cm^{-1}

Anal. Calcd for $\text{C}_{26}\text{H}_{33}\text{N}_3\text{O}-\text{C}_6\text{H}_8\text{O}_7-2\text{H}_2\text{O}$: C, 60.84; H, 7.18; N, 6.65. Found: C, 61.15; H, 6.94; N, 6.50.

Preparation 31

5 **Benzyl 1-acryloyl-1,2,3,4-tetrahydro-2-quinolinecarboxylate**

To a stirred solution of benzyl 1,2,3,4-tetrahydro-2-quinolinecarboxylate [100.0 mg, 0.374 mmol, this was prepared according to known procedure: R. Nagata, *et al*, *J. Med. Chem.* **1994**, 37, 3956] in CH_2Cl_2 (5 ml) was added triethylamine (0.094 ml, 0.673 mmol) and the resulting mixture was cooled at -30°C . To the reaction mixture was
10 added chloropropionyl chloride (57.0 mg, 0.449 mmol) and was stirred at $-30^\circ\text{C} \sim -20^\circ\text{C}$ for 45min. Then to the reaction mixture was added triethylamine (0.052 ml, 0.374 mmol) and chloropropionyl chloride (47.5 mg, 0.374 mmol) and stirred for 15min at -30°C . The reaction mixture was poured into a saturated aqueous NaHCO_3 solution and extracted with CH_2Cl_2 (15 ml x 3). The extracts combined were washed
15 with brine, dried (Na_2SO_4), filtered, and concentrated. The residue was purified by preparative TLC (1 mm thick silica gel plate: n-Hexane/AcOEt:3/1) to give 93.1 mg (78 %) of the title product as pale yellow oil.

MS (EI direct) m/z : 321(M)⁺

Preparation 32

20 **2,3-Dihydro-1'-{3-[2-[(benzyloxy)carbonyl]-3,4-dihydro-1(2H)-quinolinyl]-3-oxopropyl}spiro[1H-indene-1,4'-piperidine]**

A mixture of 2,3-dihydrospiro[1H-indene-1,4'-piperidine] hydrochloride (64.9 mg, 0.290 mmol, this was prepared according to known procedure : M. S. Chambers *et al*, *J. Med. Chem.* **1992**, 35, 2033), benzyl 1-acryloyl-1,2,3,4-tetrahydro-2-
25 quinolinecarboxylate (93.1 mg, 0.290 mmol), and triethylamine (0.061 ml, 0.435 mmol) was stirred at 60°C for 15 h. Then to the reaction mixture was added triethylamine (0.061 ml, 0.435 mmol) and stirred at 90°C for 1d. The reaction mixture was poured into a saturated aqueous NaHCO_3 solution and extracted with AcOEt (20 ml x 3). The extracts combined were dried (Na_2SO_4), filtered, and
30 concentrated. The resulting residue was purified by preparative TLC (1 mm thick silica gel plate: $\text{CH}_2\text{Cl}_2/\text{MeOH}$:25/1) to afford 57.5 mg (39 %) of title product as pale yellow oil.

^1H NMR (270 MHz, CDCl_3) δ 7.34-7.13 (13H, m), 5.31-5.25 (1H, m), 5.11 (2H, s), 2.89-2.50 (11H, m), 2.16-2.12 (2H, m), 1.98-1.73 (5H, m), 1.50-1.46 (2H, m)

MS (EI direct) m/z : 508(M) $^+$

Preparation 33

5 **2,3-Dihydro-1'-[3-{2-carboxy-3,4-dihydro-1(2*H*)-quinolinyl}-3-oxopropyl]spiro[1*H*-indene-1,4'-piperidine]**

To a stirred solution of 2,3-dihydro-1'-{3-[2-[(benzyloxy)carbonyl]-3,4-dihydro-1(2*H*)-quinolinyl]-3-oxopropyl}spiro[1*H*-indene-1,4'-piperidine] (57.5 mg, 0.113 mmol) in THF (0.5 ml) and MeOH (0.5 ml) was added 2N NaOH (0.23 ml, 0.460 mmol) at room temperature. After 2 h stirring at room temperature, the reaction mixture was dissolved to AcOEt, washed with 1N-HCl (4 ml). The extracts combined were dried (Na_2SO_4), filtered, and concentrated to give 49.0 mg (100 %) of crude compound as a white solid.

MS (ESI positive) m/z : 419 (M+H) $^+$

15 MS (ESI negative) m/z : 417 (M-H) $^+$

Example 80

2,3-Dihydro-1'-[3-[2-(aminocarbonyl)-3,4-dihydro-1(2*H*)-quinolinyl]-3-oxopropyl]spiro[1*H*-indene-1,4'-piperidine] citrate

To a stirred suspension of 2,3-dihydro-1'-[3-{2-carboxy-3,4-dihydro-1(2*H*)-quinolinyl}-3-oxopropyl]spiro[1*H*-indene-1,4'-piperidine] (49.0 mg, 0.117 mmol) in MeCN (6 ml) was added 1,1'-carbonyldiimidazole (22.7 mg, 0.140 mmol) and triethylamine (0.020 ml, 0.140 mmol) at room temperature and resulting mixture was stirred at 70°C for 2 h. To a reaction mixture was added 25 % NH_4OH (1.5 ml) and stirred at 70°C for 2 h. Then the reaction mixture was diluted with saturated aqueous NaHCO_3 solution, and extracted with CH_2Cl_2 (20 ml x 3). The extracts combined were dried (Na_2SO_4), filtered, and concentrated. The residue was purified by preparative TLC (1 mm thick plate, $\text{CH}_2\text{Cl}_2/\text{MeOH}$:10/1, 2 times developed) to afford 17.4 mg (36 %) of free base as colorless oil.

^1H NMR (270 MHz, CDCl_3) δ 7.21-7.15 (8H, m), 6.68 (2H, br), 5.25-5.19 (1H, m), 2.90-1.76 (18H, m), 1.51-1.46 (2H, m)

30 MS (ESI positive) m/z : 418 (M+H) $^+$

This was dissolved in mixed solvent of CH₂Cl₂ (1 ml) and MeOH (1 ml) followed by addition of citric acid (7.3 mg, 0.038 mmol) and resulting mixture was stirred for 2h. After concentration, the residue was solidified by adding CH₂Cl₂-hexane. The resulting solid was collected by filtration and washed with ether to give 18.2 mg of citrate as an yellow amorphous solid.

IR(KBr): 2937, 2575, 1653, 1396, 1204, 760 cm⁻¹

Anal. Calcd for C₂₆H₃₁N₃O₂·C₆H₈O₇·1.5H₂O: C, 60.37; H, 6.65; N, 6.60. Found: C, 60.36; H, 6.41; N, 6.46

Example 81

2,3-Dihydro-1'-[3-((2S)-2-[(4-hydroxy-1-piperidiny]carbonyl)-2,3-dihydro-1H-indol-1-yl]-3-oxopropyl]spiro[1H-indene-1,4'-piperidine] citrate

A mixture of 2,3-dihydro-1'-[3-(2-(S)-carboxyindolin-1-yl)-3-oxopropyl]spiro[1H-indene-1,4'-piperidine] (70.0 mg, 0.173 mmol, this was prepared in Preparation 9), 4-hydroxypiperidine (52.5 mg, 0.519 mmol), WSC (66.3 mg, 0.346 mmol), HOBt (46.8 mg, 0.346 mmol), and triethylamine (72 µl, 0.519 mmol) in CH₂Cl₂ (5 ml) – DMF (5 ml) – THF (1 ml) was stirred at room temperature for 21 h. The reaction mixture was diluted with saturated aqueous NaHCO₃ solution and extracted with CH₂Cl₂. The extracts combined were dried (Na₂SO₄), filtered, and concentrated. The residue was purified by preparative TLC (1 mm thick plate, AcOEt/PrOH/25%NH₄OH:200/40/15) to give 63.5 mg (75 %) of free base as a white solid. This compound showed broadened spectra in proton NMR.

This was converted to citric acid salt similar to that described in Example 34 to give 76.1 mg of citrate as a white solid.

MS (ESI positive) m/z: 488 (M+H)⁺

IR(KBr): 3393, 2943, 1728, 1653, 1213, 758cm⁻¹

Anal. Calcd for C₃₀H₃₇N₃O₃·C₆H₈O₇·0.2H₂O·0.5CH₂Cl₂: C, 60.40; H, 6.44; N, 5.79. Found: C, 60.18; H, 6.06; N, 5.81

Example 82

2,3-Dihydro-1'-[3-((2S)-2-[[4-(aminocarbonyl)-1-piperidiny]carbonyl]-2,3-dihydro-1H-indol-1-yl)-3-oxopropyl]spiro[1H-indene-1,4'-piperidine] citrate

This was prepared according to the procedure described in Example 81 using

isonipecotamide instead of 4-hydroxypiperidine. 58.5 mg (66 %) of free base was obtained as yellow oil. This compound showed broadened spectra in proton NMR.

This was converted to citric acid salt similar to that described in Example 34 to give 66.5 mg of citrate as a white solid.

5 MS (ESI positive) m/z: 515 (M+H)⁺

IR(KBr): 3366, 2932, 1719, 1601, 1211, 760cm⁻¹

Anal. Calcd for C₃₁H₃₈N₄O₃·C₆H₈O₇·2H₂O: C, 59.83; H, 6.78; N, 7.54. Found: C, 59.73; H, 6.53; N, 7.53

Example 83

10 **2,3-Dihydro-1'-{3-oxo-3-[(2S)-2-(1-piperazinylcarbonyl)-2,3-dihydro-1H-indol-1-yl]propyl}spiro[1H-indene-1,4'-piperidine] citrate**

This was prepared according to the procedure described in Example 81 using Boc piperazine instead of 4-hydroxypiperidine followed by removal of Boc group by treatment of TFA and basic workup. 32.1 mg (30 %) of free base was obtained as pale
15 yellow oil. This compound showed broadened spectra in proton NMR except for the following peaks.

¹H NMR (270 MHz, CDCl₃) δ 8.32-8.30 (0.3H, m), 7.03-6.98 (1H, m), 5.50-5.47 (0.5H, m), 2.52 (1H, m), 2.26 (2H, m), 1.59-1.54 (2H, m)

This was converted to citric acid salt similar to that described in Example 34 to give
20 39.7 mg of citrate as a white solid.

MS (ESI positive) m/z: 473 (M+H)⁺

IR(KBr): 3422, 2941, 1653, 1034, 758cm⁻¹

Anal. Calcd for C₂₉H₃₆N₄O₂·C₆H₈O₇·1.7H₂O: C, 60.45; H, 6.87; N, 8.06. Found: C, 60.44; H, 6.64; N, 7.89

25

Example 84

2,3-Dihydro-1'-(3-oxo-3-{(2S)-2-[(4-pyridinylamino)carbonyl]-2,3-dihydro-1H-indol-1-yl}propyl)spiro[1H-indene-1,4'-piperidine] citrate

This was prepared according to the procedure described in Example 81 using 4-aminopyridine instead of 4-hydroxypiperidine. 50.7 mg (61 %) of free base was
30 obtained as yellow oil. This compound showed broadened spectra in proton NMR except for the following peaks.

^1H NMR (270 MHz, CDCl_3) δ 9.77 (0.2H, br), 8.48-8.45 (2H, m), 7.47-7.45 (2H, m), 2.32-2.23 (2H, m), 2.02-1.89 (5H, m), 1.58-1.54 (2H, m).

This was converted to citric acid salt similar to that described in Example 34 to give 55.3 mg of citrate as a white solid.

5 MS (ESI positive) m/z : 481($\text{M}+\text{H}$) $^+$

MS (ESI negative) m/z : 479($\text{M}-\text{H}$) $^+$

IR(KBr): 3393, 2932, 1717, 1597, 1184, 835, 758 cm^{-1}

Anal. Calcd for $\text{C}_{30}\text{H}_{32}\text{N}_4\text{O}_2\cdot\text{C}_6\text{H}_8\text{O}_7\cdot 2\text{H}_2\text{O}$: C, 61.01; H, 6.26; N, 7.90. Found: C, 61.19; H, 6.04; N, 7.68.

10

Example 85

2,3-Dihydro-1'-(3-oxo-3-((2S)-2-[(1,3-thiazol-2-ylamino)carbonyl]-2,3-dihydro-1H-indol-1-yl)propyl)spiro[1H-indene-1,4'-piperidine] citrate

This was prepared according to the procedure described in Example 81 using 2-aminothiazole instead of 4-hydroxypiperidine. 61.2 mg (73 %) of free base was
15 obtained as yellow oil. This compound showed broadened spectra in proton NMR except for the following peaks.

^1H NMR (270 MHz, CDCl_3) δ 7.45-7.43 (1H, m), 7.25-7.07(8H, m), 6.97-6.96 (1H, m), 2.31-2.23 (2H, m), 2.03-1.90 (5H, m), 1.56-1.51 (2H, m)

This was converted to citric acid salt similar to that described in Example 34 to give
20 66.1 mg of citrate as a white solid.

MS (ESI positive) m/z : 487($\text{M}+\text{H}$) $^+$

MS (ESI negative) m/z : 485($\text{M}-\text{H}$) $^+$

IR(KBr): 2941, 1541, 758 cm^{-1}

Anal. Calcd for $\text{C}_{28}\text{H}_{30}\text{N}_4\text{O}_2\text{S}\cdot\text{C}_6\text{H}_8\text{O}_7\cdot 1.5\text{H}_2\text{O}$: C, 57.86; H, 5.86; N, 7.94.
25 Found: C, 57.66; H, 5.80; N, 7.71

Example 86

2,3-Dihydro-1'-(3-((2S)-2-[(4-amino-1-piperidinyl)carbonyl]-2,3-dihydro-1H-indol-1-yl)-3-oxopropyl)spiro[1H-indene-1,4'-piperidine] citrate

This was prepared according to the procedure described in Example 81 using 4-*tert*-
30 butoxycarbonylaminopiperidine (This was prepared according to known procedure: Carling, Robert W. *et al*, *J. Med. Chem.*, 1999, 42, 2706) instead of 4-

hydroxypiperidine followed by removal of Boc group by treatment of TFA and basic workup. 81.8 mg (66 %) of free base was obtained as pale yellow oil.

This compound showed broadened spectra in proton NMR.

This was converted to citric acid salt similar to that described in Example 34 to give 96.2 mg of citrate as a white solid.

MS (ESI positive) m/z : 487 ($M+H$)⁺

IR(KBr): 2937, 1638, 1219, 758 cm^{-1}

Anal. Calcd for C₃₀H₃₈N₄O₂·C₆H₈O₇·2H₂O: C, 60.49; H, 7.05; N, 7.84. Found: C, 60.41; H, 6.95; N, 7.79

Example 87

2,3-Dihydro-1'-[3-((2S)-2-{[4-(dimethylamino)-1-piperidinyl]carbonyl}-2,3-dihydro-1H-indol-1-yl)-3-oxopropyl]spiro[1H-indene-1,4'-piperidine] citrate

To a stirred solution of 2,3-dihydro-1'-[3-{2-(S)-2-[(4-amino-1-piperidinyl)carbonyl]-2,3-dihydro-1H-indol-1-yl}-3-oxopropyl]spiro[1H-indene-1,4'-piperidine] (66.0 mg, 0.136 mmol, this was prepared in Example 86.) and 37% formic acid (51 μ l, 0.680 mmol) in MeCN (4 ml) was added sodium cyanoborohydride (13.7 mg, 0.218 mmol) at 0°C and resulting mixture was stirred at room temperature for 18 h. Then, to a reaction mixture was added sodium cyanoborohydride (13.7 mg, 0.218 mmol) and stirred at room temperature for 22 h. Then the reaction mixture was diluted with saturated aqueous NaHCO₃ solution, and extracted with CH₂Cl₂ (20 ml x 3). The extracts combined were dried (Na₂SO₄), filtered, and concentrated. The residue was purified by preparative TLC (1 mm thick plate, AcOEt/PrOH/25%NH₄OH:10/2/1, 2 times developed) to afford 36.9 mg (53 %) of free base as pale yellow oil. This compound showed broadened spectra in proton NMR.

This was converted to citric acid salt similar to that described in Example 34 to give 44.8 mg of citrate as a white solid.

MS (ESI positive) m/z : 515 ($M+H$)⁺

IR(KBr):3422, 2937, 1653, 762 cm^{-1}

Anal. Calcd for C₃₂H₄₂N₄O₂·C₆H₈O₇·1.7H₂O: C, 61.89; H, 7.30; N, 7.60. Found: C, 61.94; H, 7.19; N, 7.84

Example 88**2,3-Dihydro-1'-(3-oxo-3-((2S)-2-[(2-pyridinylamino)carbonyl]-2,3-dihydro-1H-indol-1-yl)propyl)spiro[1H-indene-1,4'-piperidine] citrate**

This was prepared according to the procedure described in Example 81 using 2-aminopyridine instead of 4-hydroxypiperidine. 14.6 mg (17 %) of free base was obtained as yellow oil. This compound showed broadened spectra in proton NMR except for the following peaks.

¹H NMR (270 MHz, CDCl₃) δ 8.26-8.06 (3H, m), 7.66 (1H, m), 7.45-7.39 (1H, m), 6.67-6.62 (1H, m), 6.51-6.48 (1H, m), 2.26 (2H, m), 1.55 (2H, m)

This was converted to citric acid salt similar to that described in Example 34 to give 15.5 mg of citrate as a white solid.

MS (ESI positive) m/z: 481(M+H)⁺

MS (ESI negative) m/z: 479(M-H)⁺

IR(KBr): 2936, 1701, 1437, 758 cm⁻¹

Anal. Calcd for C₃₀H₃₂N₄O₂·C₆H₈O₇·1H₂O: C, 62.60; H, 6.13; N, 8.11. Found: C, 62.75; H, 6.24; N, 7.78

Example 89**2,3-Dihydro-1'-(3-((2S)-2-[(diethylamino)carbonyl]-2,3-dihydro-1H-indol-1-yl)-3-oxopropyl)spiro[1H-indene-1,4'-piperidine] citrate**

This was prepared according to the procedure described in Example 81 using diethylamine instead of 4-hydroxypiperidine. 91.5 mg (67 %) of free base was obtained as yellow oil. This compound showed broadened spectra in proton NMR except for the following peaks.

¹H NMR (270 MHz, CDCl₃) δ 8.31-8.28 (0.3H, m), 7.02-6.96 (1H, m), 2.04-1.94 (4H, m), 1.59-1.54 (2H, m).

This was converted to citric acid salt similar to that described in Example 34 to give 118.1 mg of citrate as a white solid.

MS (ESI positive) m/z: 460(M+H)⁺

IR(KBr): 1728, 1645, 757 cm⁻¹

Anal. Calcd for C₂₉H₃₇N₃O₂·C₆H₈O₇·1.5H₂O: C, 61.93; H, 7.13; N, 6.19. Found: C, 62.23; H, 7.39; N, 5.87

Example 90**2,3-Dihydro-1'-[3-((2S)-2-[[ethyl(methyl)amino]carbonyl]-2,3-dihydro-1H-indol-1-yl)-3-oxopropyl]spiro[1H-indene-1,4'-piperidine] citrate**

This was prepared according to the procedure described in Example 81 using N-ethylmethylaniline instead of 4-hydroxypiperidine. 40.3 mg (30 %) of free base was obtained as colorless oil. This compound showed broadened spectra in proton NMR except for the following peaks.

¹H NMR (270 MHz, CDCl₃) δ 8.31-8.28 (0.3H, m), 7.02-6.97 (1H, m), 2.05-1.99 (4H,m), 1.60-1.56 (2H, m).

This was converted to citric acid salt similar to that described in Example 34 to give 45.6 mg of citrate as a white solid.

MS (ESI positive) m/z: 446(M+H)⁺

IR(KBr):3435, 2937, 1728, 1653, 1485, 1414, 758cm⁻¹

Anal. Calcd for C₂₈H₃₅N₃O₂-C₆H₈O₇-1H₂O: C, 62.28; H, 6.92; N, 6.41. Found: C, 62.05; H, 7.02; N, 6.04

Preparation 34**2,3-Dihydro-1'-[3-ethoxy-1-methyl-3-oxopropyl]spiro[1H-indene-1,4'-piperidine]**

To a stirred solution of 2,3-dihydrospiro[1H-indene-1,4'-piperidine](243.5 mg, 1.300 mmol, this was prepared according to known procedure : M. S. Chambers *et al*, *J. Med. Chem.* 1992, 35, 2033) and ethylacetoacetate (338.4 mg, 2.600 mmol) in CH₂Cl₂ (20 ml) was added sodium triacetoxyborohydride (826.6 mg, 3.900 mmol) and acetic acid (0.22 ml, 3.90 mmol) at 0°C. Then the reaction mixture was stirred at room temperature for 8h. Then to the reaction mixture was added ethylacetoacetate (169.2 mg, 1.300 mmol), sodium triacetoxyborohydride (413.3 mg, 1.950 mmol) and acetic acid (0.11 ml, 1.950 mmol) in CH₂Cl₂ (10 ml) and stirred for 14 h at room temperature. Then to the reaction mixture was added ethylacetoacetate (169.2 mg, 1.300 mmol), sodium triacetoxyborohydride (413.3 mg, 1.950 mmol) and acetic acid (0.11 ml, 1.950 mmol) and stirred at room temperature for 9 h. Then to the reaction mixture was added ethylacetoacetate (169.2 mg, 1.300 mmol), sodium triacetoxyborohydride (413.3 mg, 1.950 mmol) and acetic acid (0.11 ml, 1.950 mmol) and stirred at room temperature for 23 h. The reaction mixture was poured into a

saturated aqueous NaHCO₃ solution and extracted with CH₂Cl₂ (50 ml x 3). The extracts combined were washed with H₂O, dried (Na₂SO₄), filtered, and concentrated. The residue was purified by silica gel column chromatography (n-Hexane/AcOEt;3/1 as eluent) to afford 194.9 mg (50 %) of title compound as colorless oil. However,
5 this product was contained ethyl acetoacetate.

It could not be assigned in proton NMR except for the following peaks.

¹H NMR (270 MHz, CDCl₃) δ 7.21-7.13 (4H, m), 3.26-3.16 (1H, m), 2.91-2.61 (7H, m), 2.27 (1H, dd, J = 14.2, 8.4 Hz), 2.06-1.83 (5H, m), 1.57-1.52 (2H, m), 1.12 (3H, d, J = 6.6 Hz).

10

Preparation 35

2,3-Dihydro-1'-[2-carbonyl-1-methylethyl]spiro[1*H*-indene-1,4'-piperidine] hydrochloride

This was prepared according to the procedure described in Preparation 2 using 2,3-dihydro-1'-[3-ethoxy-1-methyl-3-oxopropyl]spiro[1*H*-indene-1,4'-piperidine] (194.9
15 mg, 0.647 mmol) instead of 2,3-dihydro-1'-[2-(ethoxycarbonyl)ethyl]spiro[1*H*-indene-1,4'-piperidine]. 49.3 mg (25 %) of title compound was obtained as a white solid.

MS (ESI positive) m/z : 274(M+H)⁺

MS (ESI negative) m/z : 272(M-H)⁺

Example 91

2,3-Dihydro-1'-[3-(2,3-dihydro-1*H*-indol-1-yl)-1-methyl-3-oxopropyl]spiro[1*H*-indene-1,4'-piperidine] citrate

This was prepared according to the procedure described in Preparation 3 using 2,3-dihydro-1'-[2-carbonyl-1-methylethyl]spiro[1*H*-indene-1,4'-piperidine] hydrochloride (24.6 mg, 0.079 mmol) instead of 2,3-dihydro-1'-[2-(carboxy)ethyl]spiro[1*H*-indene-
25 1,4'-piperidine] hydrochloride. 25.9 mg (87 %) of free base was obtained as yellow oil.

This was converted to citric acid salt similar to that described in Example 34 to give 29.5 mg of citrate as a white solid.

¹H NMR (300 MHz, CDCl₃) δ 8.27-8.24 (1H, m), 7.23-7.13 (6H, m), 7.05-6.99 (1H, m), 4.15-4.09 (2H, m), 3.42 (1H, br), 3.24-3.19 (2H, m), 2.93-2.85 (5H, m), 2.54-2.38
30 (3H, m), 2.04-1.92 (4H, m), 1.61-1.56 (2H, m), 1.23 (3H, d, J = 6.6 Hz)

MS (ESI positive) m/z: 375(M+H)⁺

IR(KBr):2943, 1728, 1655, 1595, 1483, 1427, 758cm⁻¹

Anal. Calcd for C₂₅H₃₀N₂O-C₆H₈O₇-1.2H₂O: C, 63.29; H, 6.92; N, 4.76. Found: C, 63.25; H, 6.95; N, 4.65.

5

Preparation 36

1-(3-{*tert*-Butyl(dimethyl)silyl}oxy)propyl)-3,4-dihydro-2(1*H*)-quinolinone

To a stirred solution of NaH [326.0 mg, 8.15 mmol, 60 % oil dispersion in mineral oil, which was removed by washing with n-hexane (5 ml x 2) before use] and 3,4-dihydro-2(1*H*)-quinolinone (1.00 g, 6.79 mmol) in DMF (140 ml) was added a solution of (3-bromopropoxy)-*tert*-butyldimethylsilane (3.1 ml, 13.6 mmol) in DMF (20 ml) at 0 °C. The reaction mixture was stirred at 0 °C to room temperature for 3 h. The reaction mixture was cooled to 0 °C and NaHCO₃ solution was added to the reaction mixture, then extracted with AcOEt (100 ml x 3). The extracts combined were washed with H₂O, dried (Na₂SO₄), and filtered. The filtrate was evaporated in vacuo to afford 2.96 g of crude product, which was purified by silica gel column chromatography (n-Hexane/AcOEt : 4/1 as eluent) to give 1.97 g (91 %) of the title compound as pale yellow oil.

¹H NMR (300 MHz, CDCl₃) δ 7.26-7.14 (3H, m), 7.02-6.97 (1H, m), 4.05-4.00 (2H, m), 3.71 (2H, t, J = 5.9 Hz), 2.91-2.86 (2H, m), 2.66-2.61 (2H, m), 1.94-1.85 (2H, m), 0.93 (9H, s), 0.072 (6H, s)

20

Preparation 37

1-(3-Hydroxypropyl)-3,4-dihydro-2(1*H*)-quinolinone

To a stirred solution of 1-(3-{*tert*-butyl(dimethyl)silyl}oxy)propyl)-3,4-dihydro-2(1*H*)-quinolinone (1.97 g, 6.18 mmol) in THF (50 ml) was added tetrabutylammonium fluoride (12.4 ml, 12.36 mmol; 1M solution in THF) at 0°C. After 1 h stirring at room temperature, H₂O was added to the reaction mixture, then extracted with AcOEt (50 ml x 3). The extracts combined were dried (Na₂SO₄) and filtered. The filtrate was evaporated in vacuo to afford 2.08 g of crude product, which was purified by silica gel column chromatography (n-Hexane/AcOEt : 1/1 to 0/1 as eluent) to give 1.33 g (quant.) of the title compound as pale brown oil.

30

¹H NMR (300 MHz, CDCl₃) δ 7.29-7.17 (2H, m), 7.10-7.00 (2H, m), 4.16-4.08 (2H,

m), 3.57-3.55 (2H, m), 3.36 (1H, m), 2.96-2.90 (2H, m), 2.73-2.67 (2H, m), 1.93-1.84 (2H, m)

Preparation 38

1-(3-Bromopropyl)-3,4-dihydro-2(1H)-quinolinone

5 To a stirred solution of 1-(3-hydroxypropyl)-3,4-dihydro-2(1H)-quinolinone (100.0 mg, 0.487 mmol) in CH₂Cl₂ (5 ml) was added triphenylphosphine (153.2 mg, 0.584 mmol) and carbon tetrabromide (242.4 mg, 0.731 mmol) at 0°C. After 1.5 h stirring at room temperature, the reaction mixture was diluted with saturated aqueous NaHCO₃ solution, and extracted with CH₂Cl₂ (15 ml x 3), dried (Na₂SO₄) and filtered. The
10 filtrate was evaporated in vacuo to afford 457.8 mg of crude product, which was purified by silica gel column chromatography (n-Hexane/AcOEt : 3/1 to 1/1 as eluent) to give 113.6 mg (87 %) of the title compound as colorless oil.

¹H NMR (300 MHz, CDCl₃) δ 7.29-7.24 (1H, m), 7.19-7.16 (1H, m), 7.09-6.99 (2H, m), 4.11-4.06 (2H, m), 3.48 (2H, t, J = 6.4 Hz), 2.92-2.88 (2H, m), 2.67-2.62 (2H, m),
15 2.28-2.19 (2H, m)

Example 92

1'-[3-(2-Oxo-3,4-dihydro-1(2H)-quinolinyl)propyl]spiro[isobenzofuran-1(3H),4'-piperidine] citrate

A mixture of spiro[isobenzofuran-1(3H),4'-piperidine] hydrochloride [79.7 mg, 0.353
20 mmol, this was prepared according to known procedure : Hirokazu Kubota *et.al. Chem. Pharm. Bull.*, 1998, 46, 351], 1-(3-bromopropyl)-3,4-dihydro-2(1H)-quinolinone (113.6 mg, 0.424 mmol), K₂CO₃ (146.4 mg, 1.059 mmol), and KI (29.4 mg, 0.177 mmol) in MeCN (10 ml) was refluxed with stirring for 16 h. After cooling down to room temperature, water (30 ml) was added to the reaction mixture and extracted with
25 CH₂Cl₂ (20 ml x 3). The extracts combined were dried (Na₂SO₄), filtered, and concentrated to give 161.8 mg of crude product. This was purified by silica gel column chromatography (CH₂Cl₂/MeOH: 20/1 as an eluent). Then extracted product was purified again by preparative TLC (1 mm thick plate, CH₂Cl₂/MeOH:15/1) to afford 74.3 mg (56 %) of free base as colorless oil.

30 ¹H NMR (270 MHz, CDCl₃) δ 7.30-7.09 (7H, m), 7.03-6.97 (1H, m), 5.06 (2H, s), 4.05-4.00 (2H, m), 2.92-2.87 (4H, m), 2.67-2.62 (2H, m), 2.55-2.38 (4H, m), 2.06-1.86

(4H, m), 1.80-1.76 (2H, m)

This was converted to citric acid salt similar to that described in Example 34 to give 103.3 mg of citrate as a white solid.

MS (ESI positive) m/z: 377(M+H)⁺

5 IR(KBr): 1387, 1188, 1045, 760cm⁻¹

Anal. Calcd for C₂₄H₂₈N₂O₂·C₆H₈O₇·1.2H₂O·0.17C₆H₁₄·0.25CH₂Cl₂: C, 60.03; H, 6.60; N, 4.47. Found: C, 59.97; H, 6.36; N, 4.46

Example 93

1'-[3-(2-Oxo-3,4-dihydro-1(2*H*)-quinolinyl)propyl]spiro[1*H*-indene-1,4'-
10 piperidine] citrate

This was prepared according to the procedure described in Example 92 using spiro[1*H*-indene-1,4'-piperidine] hydrochloride (This was prepared according to known procedure : M. S. Chambers *et al*, *J. Med. Chem.* **1992**, 35, 2033) instead of spiro[isobenzofuran-1(3*H*),4'-piperidine] hydrochloride. 61.4 mg (46 %) of free base
15 was obtained as pale yellow oil.

¹H NMR (270 MHz, CDCl₃) δ 7.39-7.12 (7H, m), 7.04-6.98 (1H, m), 6.84 (1H, d, J = 5.6 Hz), 6.74 (1H, d, J = 5.6 Hz), 4.07-4.02 (2H, m), 3.06-3.02 (2H, m), 2.93-2.88 (2H, m), 2.68-2.56 (4H, m), 2.42-2.34 (2H, m), 2.27-2.22 (2H, m), 1.98-1.93 (2H, m), 1.40-1.35 (2H, m)

20 This was converted to citric acid salt similar to that described in Example 34 to give 83.0 mg of citrate as a pale yellow solid.

MS (ESI positive) m/z: 373(M+H)⁺

IR(KBr):2953, 1732, 1186, 756cm⁻¹

Anal. Calcd for C₂₅H₂₈N₂O·C₆H₈O₇·3H₂O: C, 62.93; H, 6.64; N, 4.73. Found: C,
25 62.65; H, 6.53; N, 4.36

Example 94

1-Methyl-1'-[3-(2-oxo-3,4-dihydro-1(2*H*)-quinolinyl)propyl]spiro[indoline-3,4'-
piperidine] citrate

This was prepared according to the procedure described in Example 92 using 1-
30 methylspiro(indoline-3,4'-piperidine) [51.5 mg, 0.255 mmol, this was prepared according to known procedure : Efange, Simon M.N. *et al*, *J. Med. Chem.* **1997**, 40,

3905] instead of spiro[isobenzofuran-1(3*H*),4'-piperidine] hydrochloride. 48.8 mg (49 %) of free base was obtained as pale yellow oil.

¹H NMR (270 MHz, CDCl₃) δ 7.27-6.97 (6H, m), 6.72-6.67 (1H, m), 6.49-6.46 (1H, m), 4.04-3.98 (2H, m), 3.19 (2H, s), 2.92-2.87 (4H, m), 2.76 (3H, s), 2.67-2.62 (2H, m),
5 2.50-2.45 (2H, m), 2.17-2.08 (2H, m), 2.00-1.84 (4H, m), 1.75-1.71 (2H, m)

This was converted to citric acid salt similar to that described in Example 34 to give 67.5 mg of citrate as a pale yellow solid.

MS (ESI positive) m/z: 390(M+H)⁺

IR(KBr):2951, 1717, 1387, 1192, 756cm⁻¹

10 Anal. Calcd for C₂₅H₃₁N₃O·C₆H₈O₇·0.8H₂O·0.1C₆H₁₄·0.2CH₂Cl₂: C, 61.52; H, 6.75; N, 6.77. Found: C, 61.52; H, 6.90; N, 6.39

Preparation 39

1'-(3-Hydroxypropyl)spiro[1*H*-indene-1,4'-piperidine]

This was prepared according to the procedure described in Preparation 6 using
15 spiro[1*H*-indene-1,4'-piperidine] hydrochloride instead of 2,3-dihydrospiro[1*H*-indene-1,4'-piperidine] hydrochloride. 1.8 g (55 %) of the title product was obtained as a white solid.

¹H NMR (270 MHz, CDCl₃) δ 7.40-7.15 (4H, m), 6.82 (1H, d, J = 5.6 Hz), 6.75 (1H, d, J = 5.6 Hz), 3.87 (2H, t, J = 5.3 Hz), 3.25-3.10 (2H, m), 2.75 (2H, t, J = 5.8 Hz),
20 2.45-2.30 (2H, m), 2.23-2.05 (2H, m), 1.86-1.72 (2H, m), 1.45-1.35 (2H, m).

Preparation 40

1'-(3-Mesyloxypropyl)spiro[1*H*-indene-1,4'-piperidine]

This was prepared according to the procedure described in Preparation 7 using 1'-(3-hydroxypropyl)spiro[1*H*-indene-1,4'-piperidine] instead of 2,3-dihydro-1'-(3-hydroxypropyl)spiro[1*H*-indene-1,4'-piperidine]. 158 mg (quant) of the title product
25 was obtained as colorless oil.

¹H NMR (270 MHz, CDCl₃) δ 7.45-7.15 (4H, m), 6.83 (1H, d, J = 5.6 Hz), 6.74 (1H, d, J = 5.6 Hz), 4.35 (2H, t, J = 6.4 Hz), 3.03 (3H, s), 3.02-2.92 (2H, m), 2.59 (2H, t, J = 7.1 Hz), 2.42-2.29 (2H, m), 2.23-2.09 (2H, m), 2.07-1.94 (2H, m), 1.42-1.30 (2H, m).

30

Preparation 41

1'-[3-[3-(Hydroxymethyl)-2-oxo-1(2*H*)-quinolinyl]propyl]spiro[1*H*-indene-1,4'-

piperidine]

This was prepared according to the procedure described in Example 4 using 1'-(3-mesyloxypropyl)spiro[1*H*-indene-1,4'-piperidine] and 3-hydroxymethyl-2(1*H*)-quinolinone (this was prepared according to known procedure: M. Uchida *et al*, *Chem. Pharm. Bull.* **1985**, 33, 3775) instead of 2,3-dihydro-1'-(3-mesyloxypropyl)spiro[1*H*-indene-1,4'-piperidine] and benzothiazol-2-one. 91 mg (58 %) of the title product was obtained as a pale brown amorphous.

¹H NMR (270 MHz, CDCl₃) δ 7.64-7.54 (4H, m), 7.42-7.18 (5H, m), 6.85 (1H, d, J = 5.6 Hz), 6.75 (1H, d, J = 5.6 Hz), 4.69 (2H, s), 4.50-4.40 (2H, m), 3.10-2.98 (2H, m), 2.64 (2H, t, J = 6.9 Hz), 2.44-2.32 (2H, m), 2.27-2.12 (2H, m), 2.10-1.98 (2H, m), 1.44-1.33 (2H, m).

MS (ESI positive) m/z: 401 (M+H)⁺.

Example 95

1'-[3-[3-(Hydroxymethyl)-2-oxo-3,4-dihydro-1(2*H*)-quinolinyl]propyl]spiro[1*H*-indene-1,4'-piperidine] citrate

To a stirred solution of 1'-[3-[3-(Hydroxymethyl)-2-oxo-1(2*H*)-quinolinyl]propyl]spiro[1*H*-indene-1,4'-piperidine] (90 mg, 0.23 mmol) in toluene (4ml) was added L-selectride (1.0M THF solution, 0.67 ml) at -78°C. The resulting reaction mixture was warmed to -30°C, and stirred for 2 h. L-selectride (1.0M THF solution, 0.67 ml) was added to this mixture at -30°C, and the reaction mixture warmed to 0°C. After 1 h, this was quenched with aqueous NaHCO₃ solution and extracted with CH₂Cl₂. The extracts combined were dried (MgSO₄), filtered, and concentrated. The resulting residue was purified by preparative TLC (1 mm thick silica gel plate: CH₂Cl₂/MeOH:20/1) to afford 36 mg (40 %) of free base as a colorless amorphous.

¹H NMR (270 MHz, CDCl₃) δ 7.40-7.12 (7H, m), 7.08-6.98 (1H, m), 6.84 (1H, d, J = 5.6 Hz), 6.74 (1H, d, J = 5.6 Hz), 4.10-4.00 (2H, m), 3.89 (2H, d, J = 5.3 Hz), 3.08-2.66 (5H, m), 2.55 (2H, t, J = 7.4 Hz), 2.42-2.28 (2H, m), 2.27-2.12 (2H, m), 2.08-1.80 (2H, m), 1.44-1.32 (2H, m).

This was converted to citrate salt similar to that described in Example 34 to give 67.5 mg of the title product as a white amorphous solid.

MS (ESI positive) m/z: 403 (M+H)⁺

IR(KBr): 3358, 2943, 1728, 1651, 1601, 1464, 1394, 1186, 756 cm^{-1}

Anal. Calcd for $\text{C}_{26}\text{H}_{30}\text{N}_2\text{O}_2 \cdot \text{C}_6\text{H}_8\text{O}_7 \cdot 1.78\text{H}_2\text{O}$: C, 61.33; H, 6.68; N, 4.47.

Found: C, 60.96; H, 6.28; N, 4.28

Example 96

5 **2,3-Dihydro-1'-[3-(6-fluoro-2,3-dihydro-1*H*-indol-1-yl)-3-oxopropyl]spiro[1*H*-indene-1,4'-piperidine] formate**

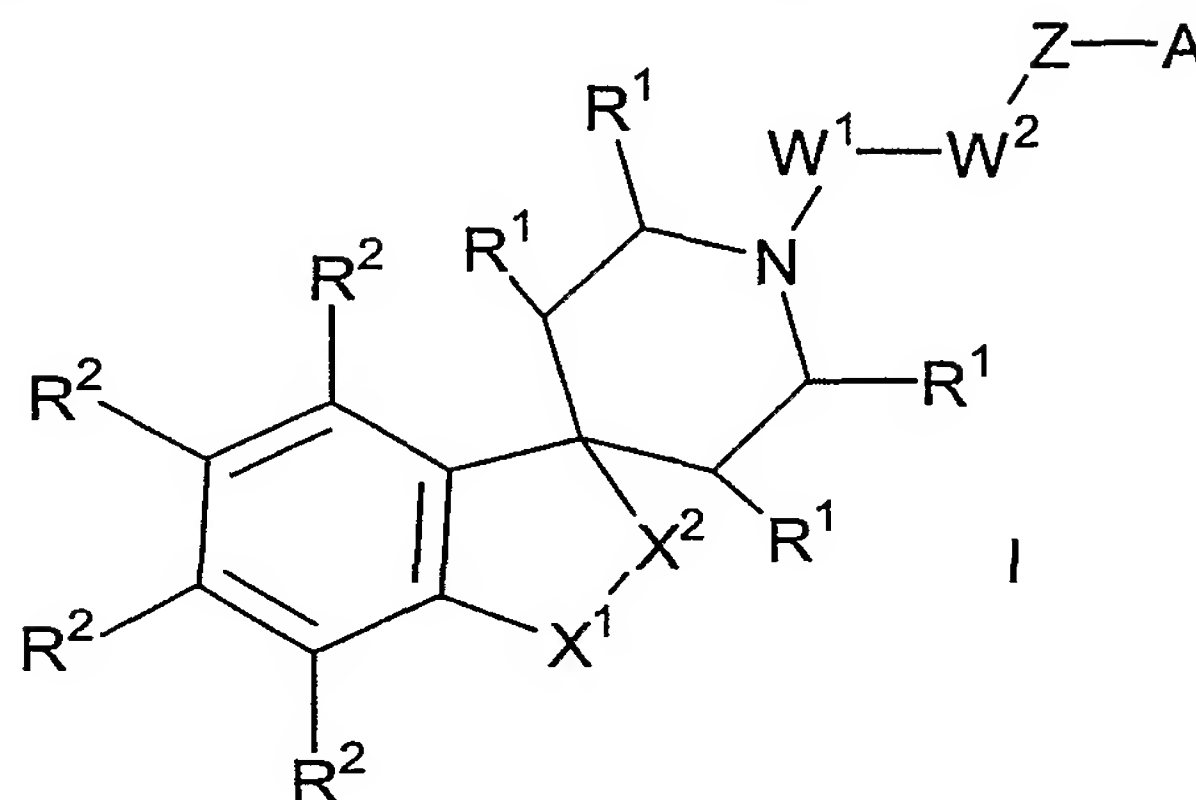
To 6-fluoro-2,3-dihydro-1*H*-indole (75 μmol) was added the mixture of 2,3-Dihydro-1'-[2-(carboxy)ethyl]spiro[1*H*-indene-1,4'-piperidine] hydrochloride (50 μmol , this was prepared in Preparation 2) and *i*PrNEt (125 μmol) dissolved in DCE (500 μl).
10 HBTU (60 μmol) dissolved in DCE/DMF (200 μl /300 μl) was added, then the reaction mixture was stirred at r.t. for 24 h. To this mixture was added phenylisocyanate (9 mg, 75 μmol), and the resulting mixture was stirred at rt for 1 h. The mixture was loaded onto a BondElute SCX cartridge (500 mg/3 ml) preconditioned 1 ml of MeOH. The solid-phase matrix was washed twice with 10 ml of MeOH/DCM (3/1) and then eluted
15 with 2 ml of 1M ammonia/MeOH. The eluate was concentrated to dryness by N_2 gas blow and vacuum centrifuge, providing crude product, which was purified with preparative LS/MS to give 1.5 mg (7 %) of the title product as the formate form.

MS (ESI positive) m/z : 379 ($\text{M}+\text{H}$)⁺

HPLC purity (UV210-400nm): >99%

CLAIMS

1. A compound of the following formula:



or pharmaceutically acceptable salts thereof, wherein

5 each R^1 is independently selected from hydrogen and (C_1-C_6) alkyl optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, $[(C_1-C_6)\text{alkyl}]-C(=O)-$, (C_1-C_6) alkoxy, $[(C_1-C_6)\text{alkoxy}]-C(=O)-$, $R^{a1}R^{a2}N-$ and $R^{a3}R^{a4}N-C(=O)-$, wherein R^{a1} , R^{a2} , R^{a3} and R^{a4} are independently selected from hydrogen, (C_1-C_6) alkyl, $[(C_1-C_6)\text{alkyl}]-C(=O)-$, $[(C_1-C_6)\text{alkoxy}]-C(=O)-$ and $[(C_1-$
 10 $C_6)\text{alkyl}]-SO_2-$; or

two R^1 groups taken together form $-CH_2-$ or $-(CH_2)_2-$ and the remaining R^1 groups are defined as above;

each R^2 is independently selected from

hydrogen; halo; hydroxy; (C_1-C_6) alkyl optionally substituted with one to three
 15 substituents independently selected from halo, hydroxy, carboxy, $[(C_1-C_6)\text{alkyl}]-C(=O)-$, (C_1-C_6) alkoxy, $[(C_1-C_6)\text{alkoxy}]-C(=O)-$, $R^{a1}R^{a2}N-$ and $R^{a3}R^{a4}N-C(=O)-$, wherein R^{a1} , R^{a2} , R^{a3} and R^{a4} are independently selected from hydrogen, (C_1-C_6) alkyl, $[(C_1-C_6)\text{alkyl}]-C(=O)-$, $[(C_1-C_6)\text{alkoxy}]-C(=O)-$ and $[(C_1-C_6)\text{alkyl}]-SO_2-$; (C_1-C_6) alkoxy optionally substituted with one to three substituents independently
 20 selected from halo, hydroxy, carboxy, $[(C_1-C_6)\text{alkyl}]-C(=O)-$, (C_1-C_6) alkoxy, $[(C_1-C_6)\text{alkoxy}]-C(=O)-$, $R^{a5}R^{a6}N-$ and $R^{a7}R^{a8}N-C(=O)-$, wherein R^{a5} , R^{a6} , R^{a7} and R^{a8} are independently selected from hydrogen, (C_1-C_6) alkyl, $[(C_1-C_6)\text{alkyl}]-C(=O)-$, $[(C_1-C_6)\text{alkoxy}]-C(=O)-$ and $[(C_1-C_6)\text{alkyl}]-SO_2-$; non-, mono- and di-substituted amino wherein the substituents are independently selected from (C_1-C_6) alkyl, $[(C_1-$
 25 $C_6)\text{alkyl}]-C(=O)-$, $[(C_1-C_6)\text{alkoxy}]-C(=O)-$ and $[(C_1-C_6)\text{alkyl}]-SO_2-$;

aryl selected from phenyl and naphthyl; and four- to eight-membered heterocyclyl containing one to four hetero atoms in the ring independently selected from nitrogen, oxygen and sulfur;

X^1 and X^2 are independently selected from

- 5 $(CH_2)_{n1}$ wherein $n1$ is an integer selected from 1, 2 and 3; $C[(C_1-C_6)alkyl]$; $C-OH$; O ; NH ; S ; $C(=O)$; SO_2 ; NR^{X1} ; $N-C(=O)R^{X2}$; $N-C(=O)OR^{X3}$; and $N-C(=O)NR^{X4}R^{X5}$; wherein R^{X1} , R^{X2} , R^{X3} , R^{X4} and R^{X5} are independently $(C_1-C_6)alkyl$ optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, $[(C_1-C_6)alkyl]-C(=O)-$, $(C_1-C_6)alkoxy$, $[(C_1-C_6)alkoxy]-C(=O)-$, $R^{a1}R^{a2}N-$ and $R^{a3}R^{a4}N-C(=O)-$, wherein R^{a1} , R^{a2} , R^{a3} and R^{a4} are
10 independently selected from hydrogen, $(C_1-C_6)alkyl$, $[(C_1-C_6)alkyl]-C(=O)-$, $[(C_1-C_6)alkoxy]-C(=O)-$ and $[(C_1-C_6)alkyl]-SO_2-$; or

X^1 and X^2 taken together form $CH=CH$;

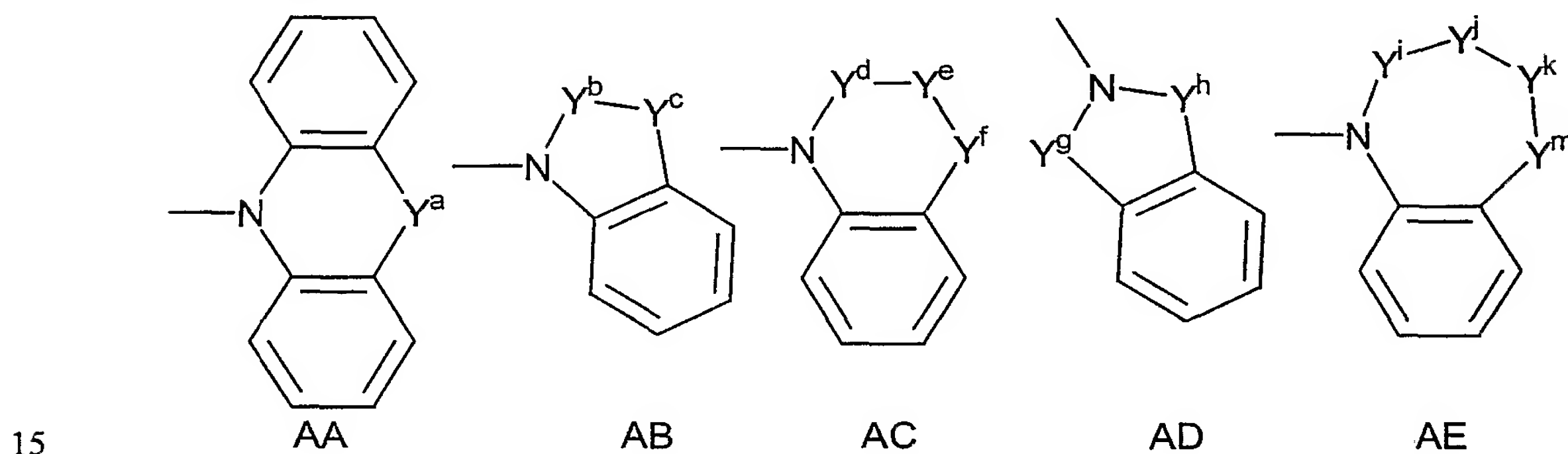
W^1 and W^2 are independently selected from $CR^{W1}R^{W2}$, wherein

- 15 R^{W1} and R^{W2} are independently selected from hydrogen; halo; hydroxy; $(C_1-C_6)alkyl$ optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, $[(C_1-C_6)alkyl]-C(=O)-$, $(C_1-C_6)alkoxy$, $[(C_1-C_6)alkoxy]-C(=O)-$, $R^{a1}R^{a2}N-$ and $R^{a3}R^{a4}N-C(=O)-$, wherein R^{a1} , R^{a2} , R^{a3} and R^{a4} are independently selected from hydrogen, $(C_1-C_6)alkyl$, $[(C_1-C_6)alkyl]-C(=O)-$,
20 $[(C_1-C_6)alkoxy]-C(=O)-$ and $[(C_1-C_6)alkyl]-SO_2-$; $(C_1-C_6)alkoxy$ optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, $[(C_1-C_6)alkyl]-C(=O)-$, $(C_1-C_6)alkoxy$, $[(C_1-C_6)alkoxy]-C(=O)-$, $R^{a5}R^{a6}N-$ and $R^{a7}R^{a8}N-C(=O)-$, wherein R^{a5} , R^{a6} , R^{a7} and R^{a8} are independently selected from hydrogen, $(C_1-C_6)alkyl$, $[(C_1-C_6)alkyl]-C(=O)-$, $[(C_1-C_6)alkoxy]-C(=O)-$ and $[(C_1-C_6)alkyl]-SO_2-$;
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- $C(=O)-[(C_1-C_6)alkyl]$ wherein said $(C_1-C_6)alkyl$ is optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, $[(C_1-C_6)alkyl]-C(=O)-$, $(C_1-C_6)alkoxy$, $[(C_1-C_6)alkoxy]-C(=O)-$, $R^{a1}R^{a2}N-$ and $R^{a3}R^{a4}N-C(=O)-$, wherein R^{a1} , R^{a2} , R^{a3} and R^{a4} are independently selected from
30 hydrogen, $(C_1-C_6)alkyl$, $[(C_1-C_6)alkyl]-C(=O)-$, $[(C_1-C_6)alkoxy]-C(=O)-$ and $[(C_1-C_6)alkyl]-SO_2-$; $C(=O)-NR^{W11}R^{W12}$ wherein R^{W11} and R^{W12} are independently selected from hydrogen and $(C_1-C_6)alkyl$ optionally substituted with one to

three substituents independently selected from halo, hydroxy, carboxy, [(C₁-C₆)alkyl]-C(=O)-, (C₁-C₆)alkoxy, [(C₁-C₆)alkoxy]-C(=O)-, R^{a1}R^{a2}N- and R^{a3}R^{a4}N-C(=O)-, wherein R^{a1}, R^{a2}, R^{a3} and R^{a4} are independently selected from hydrogen, (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-; NR^{w13}R^{w14} wherein R^{w13} and R^{w14} are independently selected from hydrogen and (C₁-C₆)alkyl optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, [(C₁-C₆)alkyl]-C(=O)-, (C₁-C₆)alkoxy, [(C₁-C₆)alkoxy]-C(=O)-, R^{a1}R^{a2}N- and R^{a3}R^{a4}N-C(=O)-, wherein R^{a1}, R^{a2}, R^{a3} and R^{a4} are independently selected from hydrogen, (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-; aryl selected from phenyl and naphthyl; and four- to eight-membered heterocyclyl containing one to four hetero atoms independently selected from nitrogen, oxygen and sulfur;

A is selected from AA; AB; AC; AD and AE:



wherein

Y^a is selected from (CH₂)_{n2} wherein n2 is an integer selected from 0, 1 and 2; C(=O); NH; O and S;

Y^b, Y^c, Y^d, Y^e, Y^f, Y^g, Y^h, Yⁱ, Y^j, Y^k and Y^m are independently selected from C(=O); CR^{y1}R^{y2}; CR^{y3}[C(=O)R^{y4}]; CR^{y3}[NR^{y5}C(=O)R^{y4}]; CR^{y3}[C(=O)NR^{y6}R^{y7}]; CR^{y3}[NR^{y6}R^{y7}]; O; S; SO₂; NH; N[(C₁-C₆)alkyl] wherein said (C₁-C₆)alkyl is optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, [(C₁-C₆)alkyl]-C(=O)-, (C₁-C₆)alkoxy, [(C₁-C₆)alkoxy]-C(=O)-, R^{a1}R^{a2}N- and R^{a3}R^{a4}N-C(=O)-, wherein R^{a1}, R^{a2}, R^{a3} and R^{a4} are independently selected from hydrogen, (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-; N-(CH₂)_{n3}-heterocyclyl wherein n3

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is an integer selected from 0, 1, 2 and 3, and said heterocyclyl contains from four to eight ring atoms one or two of which are independently selected from nitrogen, oxygen and sulfur; N-(CH₂)_{n4}-aryl wherein n4 is an integer selected from 0, 1, 2 and 3, and said aryl is selected from phenyl and naphthyl; and N-(CH₂)_{n5}-heteroaryl wherein n5 is an integer selected from 0, 1, 2 and 3, and said heteroaryl is a five to ten membered aromatic heterocyclyl containing from one to four hetero atoms independently selected from nitrogen, oxygen and sulfur; or Y^b and Y^c taken together form a group selected from CR^{Y81}=CR^{Y82}; CR^{Y83}=N and N=N; and Y^d, Y^e, Y^f, Y^g and Y^h are defined as above; wherein

10 R^{Y1}, R^{Y2} and R^{Y5} are independently selected from hydrogen; hydroxy; non-, mono- and di-substituted amino wherein the substituents are independently selected from (C₁-C₆)alkyl; [(C₁-C₆)alkyl]-C(=O)-; [(C₁-C₆)alkoxy]-C(=O)-; [(C₁-C₆)alkyl]-SO₂-; and four- to eight-membered heterocyclyl containing one to four hetero atoms independently selected from nitrogen, oxygen and sulfur,

15 wherein said heterocyclyl is optionally substituted with one to three substituents independently selected from hydroxy, (C₁-C₆)alkyl, NH₂-C(O)-, [(C₁-C₆)alkyl]-NH-C(=O)-, [(C₁-C₆)alkyl]₂-N-C(=O)-, and non-, mono- and di-substituted amino wherein the substituents are independently selected from (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-; (C₁-C₆)alkyl optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, [(C₁-C₆)alkyl]-C(=O)-, (C₁-C₆)alkoxy, [(C₁-C₆)alkoxy]-C(=O)-, R^{a1}R^{a2}N- and R^{a3}R^{a4}N-C(=O)-, wherein R^{a1}, R^{a2}, R^{a3} and R^{a4} are independently selected from hydrogen, (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-; and (C₁-C₆)alkoxy optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, [(C₁-C₆)alkyl]-C(=O)-, (C₁-C₆)alkoxy, [(C₁-C₆)alkoxy]-C(=O)-, R^{a5}R^{a6}N- and R^{a7}R^{a8}N-C(=O)-, wherein R^{a5}, R^{a6}, R^{a7} and R^{a8} are independently selected from hydrogen, (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-; or

20 R^{Y1} and R^{Y2} taken together with the carbon atom to which they are attached form spiropyrrolidiny1 or spiropiperidiny1, both of which are optionally N-

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substituted with a substituent selected from (C₁-C₆)alkyl, (C₁-C₆)alkyl-C(=O)-, [(C₁-C₆)alkyl]-C(=O)-(C₁-C₆)alkyl and aryl-(C=O)- wherein aryl is selected from phenyl and naphthyl; and R^{Y5} is defined as above;

R^{Y3} is hydrogen;

5 R^{Y4} is selected from hydroxy; (C₁-C₆)alkyl optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, [(C₁-C₆)alkyl]-C(=O)-, (C₁-C₆)alkoxy, [(C₁-C₆)alkoxy]-C(=O)-, R^{a1}R^{a2}N- and R^{a3}R^{a4}N-C(=O)-, wherein R^{a1}, R^{a2}, R^{a3} and R^{a4} are independently selected from hydrogen, (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and
10 [(C₁-C₆)alkyl]-SO₂-; and (C₁-C₆)alkoxy optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, [(C₁-C₆)alkyl]-C(=O)-, (C₁-C₆)alkoxy, [(C₁-C₆)alkoxy]-C(=O)-, R^{a5}R^{a6}N- and R^{a7}R^{a8}N-C(=O)-, wherein R^{a5}, R^{a6}, R^{a7} and R^{a8} are independently selected from hydrogen, (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and
15 [(C₁-C₆)alkyl]-SO₂-; and

R^{Y6} and R^{Y7} are independently selected from hydrogen; (C₁-C₆)alkyl optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, [(C₁-C₆)alkyl]-C(=O)-, (C₁-C₆)alkoxy, [(C₁-C₆)alkoxy]-C(=O)-, R^{a1}R^{a2}N- and R^{a3}R^{a4}N-C(=O)-, wherein R^{a1}, R^{a2}, R^{a3} and R^{a4} are
20 independently selected from hydrogen, (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-; heterocyclyl-(CH₂)_{n6}- wherein n₆ is an integer selected from 0, 1, 2, 3 and 4 and said heterocyclyl is four to eight membered containing one to three hetero atoms independently selected from nitrogen, oxygen and sulfur, wherein said heterocyclyl is optionally
25 substituted with one to three substituents independently selected from hydroxy; (C₁-C₆)alkyl; NH₂-C(=O)-; (C₁-C₆)alkyl-NH-C(=O)-; [(C₁-C₆)alkyl]₂-N-C(=O)-; and non-, mono- and di-substituted amino wherein the substituents are independently selected from (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-; and heteroaryl-(CH₂)_{n7}- wherein n₇
30 is an integer selected from 0, 1, 2, 3 and 4 and said heteroaryl is five to ten membered containing one to three hetero atoms independently selected from nitrogen, oxygen and sulfur, wherein said heteroaryl is optionally substituted

with one to three substituents independently selected from hydroxy; (C₁-C₆)alkyl; NH₂-C(O=)-; (C₁-C₆)alkyl-NH-C(=O)-; [(C₁-C₆)alkyl]₂-N-C(=O)-; and non-, mono- and di-substituted amino wherein the substituents are independently selected from (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-; or

R^{Y6} and R^{Y7} taken together with the nitrogen atom to which they are attached form a four to eight heterocyclyl optionally containing, in addition to the nitrogen atom, one to two additional hetero atoms independently selected from nitrogen, oxygen and sulfur, and said heterocyclyl is optionally substituted with one substituent selected from hydroxy; (C₁-C₆)alkyl; NH₂-C(O=)-; (C₁-C₆)alkyl-NH-C(=O)-; [(C₁-C₆)alkyl]₂-N-C(=O)-; and non-, mono- and di-substituted amino wherein the substituents are independently selected from (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-;

R^{Y81}, R^{Y82} and R^{Y83} are independently selected from R^{Y811} and R^{Y812}C(=O)- wherein R^{Y811} and R^{Y812} are independently selected from hydrogen; hydroxy; (C₁-C₆)alkyl optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, [(C₁-C₆)alkyl]-C(=O)-, (C₁-C₆)alkoxy, [(C₁-C₆)alkoxy]-C(=O)-, R^{a1}R^{a2}N- and R^{a3}R^{a4}N-C(=O)-, wherein R^{a1}, R^{a2}, R^{a3} and R^{a4} are independently selected from hydrogen, (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-; and (C₁-C₆)alkoxy optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, [(C₁-C₆)alkyl]-C(=O)-, (C₁-C₆)alkoxy, [(C₁-C₆)alkoxy]-C(=O)-, R^{a5}R^{a6}N- and R^{a7}R^{a8}N-C(=O)-, wherein R^{a5}, R^{a6}, R^{a7} and R^{a8} are independently selected from hydrogen, (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-; and

said A is optionally substituted in the fused benzene rings with one to four substituents independently selected from halo; hydroxy; mercapto; phenyl; (C₁-C₆)alkyl optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, [(C₁-C₆)alkyl]-C(=O)-, (C₁-C₆)alkoxy, [(C₁-C₆)alkoxy]-C(=O)-, R^{a1}R^{a2}N- and R^{a3}R^{a4}N-C(=O)-, wherein R^{a1}, R^{a2}, R^{a3} and R^{a4} are independently selected from hydrogen, (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-

C_6)alkyl]-SO₂-; and (C₁-C₆)alkoxy optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, [(C₁-C₆)alkyl]-C(=O)-, (C₁-C₆)alkoxy, [(C₁-C₆)alkoxy]-C(=O)-, R^{a5}R^{a6}N- and R^{a7}R^{a8}N-C(=O)-, wherein R^{a5}, R^{a6}, R^{a7} and R^{a8} are independently selected from hydrogen, (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-; and
 5 Z is selected from C(=O); (CH₂)_{n8} wherein n8 is an integer selected from 0, 1 and 2; and CHR^{Z1} wherein R^{Z1} is selected from carboxy; (C₁-C₆)alkoxy-C(=O)-; non-, mono- and di-substituted amino wherein the substituents are independently selected from (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkyl]-C(=O)-O- and [(C₁-C₆)alkyl]-SO₂-; (C₁-C₆)alkyl optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, [(C₁-C₆)alkyl]-C(=O)-, (C₁-C₆)alkoxy, [(C₁-C₆)alkoxy]-C(=O)-, R^{a1}R^{a2}N- and R^{a3}R^{a4}N-C(=O)-, wherein R^{a1}, R^{a2}, R^{a3} and R^{a4} are independently selected from hydrogen, (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-; and [C(=O)-NR^{Z11}R^{Z12}]
 10 wherein R^{Z11} and R^{Z12} are independently selected from hydrogen and (C₁-C₆)alkyl optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, [(C₁-C₆)alkyl]-C(=O)-, (C₁-C₆)alkoxy, [(C₁-C₆)alkoxy]-C(=O)-, R^{a1}R^{a2}N- and R^{a3}R^{a4}N-C(=O)-, wherein R^{a1}, R^{a2}, R^{a3} and R^{a4} are independently selected from hydrogen, (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-.
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2. A compound according to Claim 1 wherein

all R¹ are hydrogen
 each R² is independently selected from hydrogen and halo;
 25 X¹ is selected from (CH₂)_{n1} wherein n1 is an integer selected from 1, 2 and 3; O; NH; S; C(=O); SO₂; and N[(C₁-C₄)alkyl];
 X² is selected from CH₂; O; NH; S; C(=O); SO₂; and N[(C₁-C₄)alkyl]; or
 X¹ and X² taken together form CH=CH;
 W¹ and W² are independently selected from CR^{W1}R^{W2}, wherein
 30 R^{W1} and R^{W2} are independently selected from hydrogen; halo; hydroxy; (C₁-C₆)alkyl optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, [(C₁-C₆)alkyl]-C(=O)-, (C₁-C₆)alkoxy, [(C₁-

C_6)alkoxy]-C(=O)-, $R^{a1}R^{a2}N$ - and $R^{a3}R^{a4}N$ -C(=O)-, wherein R^{a1} , R^{a2} , R^{a3} and R^{a4} are independently selected from hydrogen, (C_1-C_6) alkyl, $[(C_1-C_6)alkyl]-C(=O)-$, $[(C_1-C_6)alkoxy]-C(=O)-$ and $[(C_1-C_6)alkyl]-SO_2-$; (C_1-C_6) alkoxy optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, $[(C_1-C_6)alkyl]-C(=O)-$, (C_1-C_6) alkoxy, $[(C_1-C_6)alkoxy]-C(=O)-$, $R^{a5}R^{a6}N$ - and $R^{a7}R^{a8}N$ -C(=O)-, wherein R^{a5} , R^{a6} , R^{a7} and R^{a8} are independently selected from hydrogen, (C_1-C_6) alkyl, $[(C_1-C_6)alkyl]-C(=O)-$, $[(C_1-C_6)alkoxy]-C(=O)-$ and $[(C_1-C_6)alkyl]-SO_2-$; C(=O)- $[(C_1-C_6)alkyl]$ wherein said $(C_1-C_6)alkyl$ is optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, $[(C_1-C_6)alkyl]-C(=O)-$, (C_1-C_6) alkoxy, $[(C_1-C_6)alkoxy]-C(=O)-$, $R^{a1}R^{a2}N$ - and $R^{a3}R^{a4}N$ -C(=O)-, wherein R^{a1} , R^{a2} , R^{a3} and R^{a4} are independently selected from hydrogen, $(C_1-C_6)alkyl$, $[(C_1-C_6)alkyl]-C(=O)-$, $[(C_1-C_6)alkoxy]-C(=O)-$ and $[(C_1-C_6)alkyl]-SO_2-$; C(=O)- $NR^{w11}R^{w12}$ wherein R^{w11} and R^{w12} are independently selected from hydrogen and $(C_1-C_6)alkyl$ optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, $[(C_1-C_6)alkyl]-C(=O)-$, (C_1-C_6) alkoxy, $[(C_1-C_6)alkoxy]-C(=O)-$, $R^{a1}R^{a2}N$ - and $R^{a3}R^{a4}N$ -C(=O)-, wherein R^{a1} , R^{a2} , R^{a3} and R^{a4} are independently selected from hydrogen, $(C_1-C_6)alkyl$, $[(C_1-C_6)alkyl]-C(=O)-$, $[(C_1-C_6)alkoxy]-C(=O)-$ and $[(C_1-C_6)alkyl]-SO_2-$; $NR^{w13}R^{w14}$ wherein R^{w13} and R^{w14} are independently selected from hydrogen and $(C_1-C_6)alkyl$ optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, $[(C_1-C_6)alkyl]-C(=O)-$, (C_1-C_6) alkoxy, $[(C_1-C_6)alkoxy]-C(=O)-$, $R^{a1}R^{a2}N$ - and $R^{a3}R^{a4}N$ -C(=O)-, wherein R^{a1} , R^{a2} , R^{a3} and R^{a4} are independently selected from hydrogen, $(C_1-C_6)alkyl$, $[(C_1-C_6)alkyl]-C(=O)-$, $[(C_1-C_6)alkoxy]-C(=O)-$ and $[(C_1-C_6)alkyl]-SO_2-$; aryl selected from phenyl and naphthyl; and four- to eight-membered heterocyclyl containing one to four hetero atoms independently selected from nitrogen, oxygen and sulfur;

A is AB wherein

Y^b and Y^c are independently selected from C(=O); $CR^{Y1}R^{Y2}$; $CR^{Y3}[C(=O)R^{Y4}]$; $CR^{Y3}[C(=O)NR^{Y6}R^{Y7}]$; $CR^{Y3}[NR^{Y6}R^{Y7}]$; O; S; SO_2 ; NH; N $[(C_1-C_6)alkyl]$ wherein said $(C_1-C_6)alkyl$ is optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, $[(C_1-C_6)alkyl]-C(=O)-$, $(C_1-$

C_6)alkoxy, $[(C_1-C_6)alkoxy]-C(=O)-$, $R^{a1}R^{a2}N-$ and $R^{a3}R^{a4}N-C(=O)-$, wherein R^{a1} , R^{a2} , R^{a3} and R^{a4} are independently selected from hydrogen, $(C_1-C_6)alkyl$, $[(C_1-C_6)alkyl]-C(=O)-$, $[(C_1-C_6)alkoxy]-C(=O)-$ and $[(C_1-C_6)alkyl]-SO_2-$; $N-(CH_2)_{n3}$ -heterocyclyl wherein $n3$ is an integer selected from 0, 1, 2 and 3, and said heterocyclyl contains from four to eight ring atoms one or two of which are independently selected from nitrogen, oxygen and sulfur; $N-(CH_2)_{n4}$ -aryl wherein $n4$ is an integer selected from 0, 1, 2 and 3, and said aryl is selected from phenyl and naphthyl; and $N-(CH_2)_{n5}$ -heteroaryl wherein $n5$ is an integer selected from 0, 1, 2 and 3, and said heteroaryl is a five to ten membered aromatic heterocyclyl containing from one to four hetero atoms independently selected from nitrogen, oxygen and sulfur; or

Y^b and Y^c taken together form a group selected from $CR^{Y81}=CR^{Y82}$; $CR^{Y83}=N$ and $N=N$; and Y^d , Y^e , Y^f , Y^g and Y^h are defined as above;

R^{Y1} and R^{Y2} are independently selected from hydrogen; hydroxy; non-, mono- and di-substituted amino wherein the substituents are independently selected from $(C_1-C_6)alkyl$; $[(C_1-C_6)alkyl]-C(=O)-$; $[(C_1-C_6)alkoxy]-C(=O)-$; $[(C_1-C_6)alkyl]-SO_2-$; and four- to eight-membered heterocyclyl containing one to four hetero atoms independently selected from nitrogen, oxygen and sulfur, wherein said heterocyclyl is optionally substituted with one to three substituents independently selected from hydroxy, $(C_1-C_6)alkyl$, $NH_2-C(=O)-$, $[(C_1-C_6)alkyl]-NH-C(=O)-$, $[(C_1-C_6)alkyl]_2-N-C(=O)-$, and non-, mono- and di-substituted amino wherein the substituents are independently selected from $(C_1-C_6)alkyl$, $[(C_1-C_6)alkyl]-C(=O)-$, $[(C_1-C_6)alkoxy]-C(=O)-$ and $[(C_1-C_6)alkyl]-SO_2-$; $(C_1-C_6)alkyl$ optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, $[(C_1-C_6)alkyl]-C(=O)-$, $(C_1-C_6)alkoxy$, $[(C_1-C_6)alkoxy]-C(=O)-$, $R^{a1}R^{a2}N-$ and $R^{a3}R^{a4}N-C(=O)-$, wherein R^{a1} , R^{a2} , R^{a3} and R^{a4} are independently selected from hydrogen, $(C_1-C_6)alkyl$, $[(C_1-C_6)alkyl]-C(=O)-$, $[(C_1-C_6)alkoxy]-C(=O)-$ and $[(C_1-C_6)alkyl]-SO_2-$; and $(C_1-C_6)alkoxy$ optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, $[(C_1-C_6)alkyl]-C(=O)-$, $(C_1-C_6)alkoxy$, $[(C_1-C_6)alkoxy]-C(=O)-$, $R^{a5}R^{a6}N-$ and $R^{a7}R^{a8}N-C(=O)-$, wherein R^{a5} , R^{a6} , R^{a7} and R^{a8} are independently selected from

hydrogen, (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-; or

R^{Y1} and R^{Y2} taken together with the carbon atom to which they are attached form spiropyrrolidinyl or spiropiperidinyl, both of which are optionally N-substituted with a substituent selected from (C₁-C₆)alkyl, (C₁-C₆)alkyl-C(=O)-, [(C₁-C₆)alkyl]-C(=O)-(C₁-C₆)alkyl and aryl-(C=O)- wherein aryl is selected from phenyl and naphthyl;

R^{Y3} is hydrogen;

R^{Y4} is selected from hydroxy; (C₁-C₆)alkyl optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, [(C₁-C₆)alkyl]-C(=O)-, (C₁-C₆)alkoxy, [(C₁-C₆)alkoxy]-C(=O)-, R^{a1}R^{a2}N- and R^{a3}R^{a4}N-C(=O)-, wherein R^{a1}, R^{a2}, R^{a3} and R^{a4} are independently selected from hydrogen, (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-; and (C₁-C₆)alkoxy optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, [(C₁-C₆)alkyl]-C(=O)-, (C₁-C₆)alkoxy, [(C₁-C₆)alkoxy]-C(=O)-, R^{a5}R^{a6}N- and R^{a7}R^{a8}N-C(=O)-, wherein R^{a5}, R^{a6}, R^{a7} and R^{a8} are independently selected from hydrogen, (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-; and

R^{Y5}, R^{Y6} and R^{Y7} are independently selected from hydrogen; (C₁-C₆)alkyl optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, [(C₁-C₆)alkyl]-C(=O)-, (C₁-C₆)alkoxy, [(C₁-C₆)alkoxy]-C(=O)-, R^{a1}R^{a2}N- and R^{a3}R^{a4}N-C(=O)-, wherein R^{a1}, R^{a2}, R^{a3} and R^{a4} are independently selected from hydrogen, (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-; heterocyclyl-(CH₂)_{n6}- wherein n₆ is an integer selected from 0, 1, 2, 3 and 4 and said heterocyclyl is four to eight membered containing one to three hetero atoms independently selected from nitrogen, oxygen and sulfur, wherein said heterocyclyl is optionally substituted with one to three substituents independently selected from hydroxy; (C₁-C₆)alkyl; NH₂-C(=O)-; (C₁-C₆)alkyl-NH-C(=O)-; [(C₁-C₆)alkyl]₂-N-C(=O)-; and non-, mono- and di-substituted amino wherein the substituents are independently selected from (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-

C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-; and hetroaryl-(CH₂)_{n7}- wherein n7 is an integer selected from 0, 1, 2, 3 and 4 and said heteroaryl is five to ten membered containing one to three hetero atoms independently selected from nitrogen, oxygen and sulfur, wherein said heteroaryl is optionally substituted with one to three substituents independently selected from hydroxy; (C₁-C₆)alkyl; NH₂-C(O=)-; (C₁-C₆)alkyl-NH-C(=O)-; [(C₁-C₆)alkyl]₂-N-C(=O)-; and non-, mono- and di-substituted amino wherein the substituents are independently selected from (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-; or

R^{Y6} and R^{Y7} taken together with the nitrogen atom to which they are attached form a four to eight heterocyclyl optionally containing, in addition to the nitrogen atom, one to two additional hetero atoms independently selected from nitrogen, oxygen and sulfur, and said heterocyclyl is optionally substituted with one substituent selected from hydroxy; (C₁-C₆)alkyl; NH₂-C(O=)-; (C₁-C₆)alkyl-NH-C(=O)-; [(C₁-C₆)alkyl]₂-N-C(=O)-; and non-, mono- and di-substituted amino wherein the substituents are independently selected from (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-;

R^{Y81}, R^{Y82} and R^{Y83} are independently selected from R^{Y811} and R^{Y812}C(=O)- wherein R^{Y811} and R^{Y812} are independently selected from hydrogen; hydroxy; (C₁-C₆)alkyl optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, [(C₁-C₆)alkyl]-C(=O)-, (C₁-C₆)alkoxy, [(C₁-C₆)alkoxy]-C(=O)-, R^{a1}R^{a2}N- and R^{a3}R^{a4}N-C(=O)-, wherein R^{a1}, R^{a2}, R^{a3} and R^{a4} are independently selected from hydrogen, (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-; and (C₁-C₆)alkoxy optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, [(C₁-C₆)alkyl]-C(=O)-, (C₁-C₆)alkoxy, [(C₁-C₆)alkoxy]-C(=O)-, R^{a5}R^{a6}N- and R^{a7}R^{a8}N-C(=O)-, wherein R^{a5}, R^{a6}, R^{a7} and R^{a8} are independently selected from hydrogen, (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-; and

said A is optionally substituted in the fused benzene rings with one to four substituents independently selected from halo; hydroxy; mercapto; phenyl; (C₁-C₆)alkyl optionally

- substituted with one to three substituents independently selected from halo, hydroxy, carboxy, [(C₁-C₆)alkyl]-C(=O)-, (C₁-C₆)alkoxy, [(C₁-C₆)alkoxy]-C(=O)-, R^{a1}R^{a2}N- and R^{a3}R^{a4}N-C(=O)-, wherein R^{a1}, R^{a2}, R^{a3} and R^{a4} are independently selected from hydrogen, (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-; and (C₁-C₆)alkoxy optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, [(C₁-C₆)alkyl]-C(=O)-, (C₁-C₆)alkoxy, [(C₁-C₆)alkoxy]-C(=O)-, R^{a5}R^{a6}N- and R^{a7}R^{a8}N-C(=O)-, wherein R^{a5}, R^{a6}, R^{a7} and R^{a8} are independently selected from hydrogen, (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-; and
- 10 Z is selected from C(=O); (CH₂)_{n8} wherein n8 is an integer selected from 0, 1 and 2; and CHR^{Z1} wherein
- R^{Z1} is selected from carboxy; (C₁-C₆)alkoxy-C(=O)-; non-, mono- and di-substituted amino wherein the substituents are independently selected from (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkyl]-C(=O)-O- and [(C₁-C₆)alkyl]-SO₂-; (C₁-C₆)alkyl optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, [(C₁-C₆)alkyl]-C(=O)-, (C₁-C₆)alkoxy, [(C₁-C₆)alkoxy]-C(=O)-, R^{a1}R^{a2}N- and R^{a3}R^{a4}N-C(=O)-, wherein R^{a1}, R^{a2}, R^{a3} and R^{a4} are independently selected from hydrogen, (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-; and
- 20 [C(=O)-NR^{Z11}R^{Z12}] wherein R^{Z11} and R^{Z12} are independently selected from hydrogen and (C₁-C₆)alkyl optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, [(C₁-C₆)alkyl]-C(=O)-, (C₁-C₆)alkoxy, [(C₁-C₆)alkoxy]-C(=O)-, R^{a1}R^{a2}N- and R^{a3}R^{a4}N-C(=O)-, wherein R^{a1}, R^{a2}, R^{a3} and R^{a4} are independently selected from hydrogen, (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-.
- 25

3. A compound according to Claim 2 wherein

all R¹ are hydrogen

each R² is independently selected from hydrogen and halo;

- 30 X¹ is selected from (CH₂)_{n1} wherein n1 is an integer selected from 1, 2 and 3; O; NH; S; C(=O); SO₂; and N[(C₁-C₄)alkyl];

X² is selected from CH₂; O; NH; S; C(=O); SO₂; and N[(C₁-C₄)alkyl]; or

X^1 and X^2 taken together form $CH=CH$;

W^1 and W^2 are both CH_2 ;

A is AB wherein

both Y^b and Y^c are independently selected from $C(=O)$; $CR^{Y1}R^{Y2}$; $CR^{Y3}[C(=O)R^{Y4}]$;

5 $CR^{Y3}[C(=O)NR^{Y6}R^{Y7}]$; and $CR^{Y3}[NR^{Y6}R^{Y7}]$, wherein

R^{Y1} and R^{Y2} are independently selected from hydrogen; hydroxy; non-, mono- and di-substituted amino wherein the substituents are independently selected from (C_1-C_6) alkyl; $[(C_1-C_6)alkyl]-C(=O)-$; $[(C_1-C_6)alkoxy]-C(=O)-$; $[(C_1-C_6)alkyl]-SO_2-$; and four- to eight-membered heterocyclyl containing one to
10 four hetero atoms independently selected from nitrogen, oxygen and sulfur, wherein said heterocyclyl is optionally substituted with one to three substituents independently selected from hydroxy, (C_1-C_6) alkyl, $NH_2-C(=O)-$, $[(C_1-C_6)alkyl]-NH-C(=O)-$, $[(C_1-C_6)alkyl]_2-N-C(=O)-$, and non-, mono- and di-substituted amino wherein the substituents are independently selected from
15 (C_1-C_6) alkyl, $[(C_1-C_6)alkyl]-C(=O)-$, $[(C_1-C_6)alkoxy]-C(=O)-$ and $[(C_1-C_6)alkyl]-SO_2-$; (C_1-C_6) alkyl optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, $[(C_1-C_6)alkyl]-C(=O)-$, $(C_1-C_6)alkoxy$, $[(C_1-C_6)alkoxy]-C(=O)-$, $R^{a1}R^{a2}N-$ and $R^{a3}R^{a4}N-C(=O)-$, wherein R^{a1} , R^{a2} , R^{a3} and R^{a4} are independently selected from
20 hydrogen, (C_1-C_6) alkyl, $[(C_1-C_6)alkyl]-C(=O)-$, $[(C_1-C_6)alkoxy]-C(=O)-$ and $[(C_1-C_6)alkyl]-SO_2-$; and $(C_1-C_6)alkoxy$ optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, $[(C_1-C_6)alkyl]-C(=O)-$, $(C_1-C_6)alkoxy$, $[(C_1-C_6)alkoxy]-C(=O)-$, $R^{a5}R^{a6}N-$ and $R^{a7}R^{a8}N-C(=O)-$, wherein R^{a5} , R^{a6} , R^{a7} and R^{a8} are independently selected from
25 hydrogen, (C_1-C_6) alkyl, $[(C_1-C_6)alkyl]-C(=O)-$, $[(C_1-C_6)alkoxy]-C(=O)-$ and $[(C_1-C_6)alkyl]-SO_2-$; or

R^{Y1} and R^{Y2} taken together with the carbon atom to which they are attached form spiropyrrolidinyl or spiropiperidinyl, both of which are optionally N-substituted with a substituent selected from (C_1-C_6) alkyl, $(C_1-C_6)alkyl-C(=O)-$, $[(C_1-C_6)alkyl]-C(=O)-(C_1-C_6)alkyl$ and aryl- $C(=O)-$ wherein aryl is
30 selected from phenyl and naphthyl;

R^{Y3} is hydrogen;

R^{Y4} is selected from hydroxy; (C_1-C_6) alkyl optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, $[(C_1-C_6)alkyl]-C(=O)-$, $(C_1-C_6)alkoxy$, $[(C_1-C_6)alkoxy]-C(=O)-$, $R^{a1}R^{a2}N-$ and $R^{a3}R^{a4}N-C(=O)-$, wherein R^{a1} , R^{a2} , R^{a3} and R^{a4} are independently selected from hydrogen, $(C_1-C_6)alkyl$, $[(C_1-C_6)alkyl]-C(=O)-$, $[(C_1-C_6)alkoxy]-C(=O)-$ and $[(C_1-C_6)alkyl]-SO_2-$; and $(C_1-C_6)alkoxy$ optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, $[(C_1-C_6)alkyl]-C(=O)-$, $(C_1-C_6)alkoxy$, $[(C_1-C_6)alkoxy]-C(=O)-$, $R^{a5}R^{a6}N-$ and $R^{a7}R^{a8}N-C(=O)-$, wherein R^{a5} , R^{a6} , R^{a7} and R^{a8} are independently selected from hydrogen, $(C_1-C_6)alkyl$, $[(C_1-C_6)alkyl]-C(=O)-$, $[(C_1-C_6)alkoxy]-C(=O)-$ and $[(C_1-C_6)alkyl]-SO_2-$; and

R^{Y6} and R^{Y7} are independently selected from hydrogen; $(C_1-C_6)alkyl$ optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, $[(C_1-C_6)alkyl]-C(=O)-$, $(C_1-C_6)alkoxy$, $[(C_1-C_6)alkoxy]-C(=O)-$, $R^{a1}R^{a2}N-$ and $R^{a3}R^{a4}N-C(=O)-$, wherein R^{a1} , R^{a2} , R^{a3} and R^{a4} are independently selected from hydrogen, $(C_1-C_6)alkyl$, $[(C_1-C_6)alkyl]-C(=O)-$, $[(C_1-C_6)alkoxy]-C(=O)-$ and $[(C_1-C_6)alkyl]-SO_2-$; heterocyclyl- $(CH_2)_{n6}-$ wherein $n6$ is an integer selected from 0, 1, 2, 3 and 4 and said heterocyclyl is four to eight membered containing one to three hetero atoms independently selected from nitrogen, oxygen and sulfur, wherein said heterocyclyl is optionally substituted with one to three substituents independently selected from hydroxy; $(C_1-C_6)alkyl$; $NH_2-C(=O)-$; $(C_1-C_6)alkyl-NH-C(=O)-$; $[(C_1-C_6)alkyl]_2-N-C(=O)-$; and non-, mono- and di-substituted amino wherein the substituents are independently selected from $(C_1-C_6)alkyl$, $[(C_1-C_6)alkyl]-C(=O)-$, $[(C_1-C_6)alkoxy]-C(=O)-$ and $[(C_1-C_6)alkyl]-SO_2-$; and heteroaryl- $(CH_2)_{n7}-$ wherein $n7$ is an integer selected from 0, 1, 2, 3 and 4 and said heteroaryl is five to ten membered containing one to three hetero atoms independently selected from nitrogen, oxygen and sulfur, wherein said heteroaryl is optionally substituted with one to three substituents independently selected from hydroxy; $(C_1-C_6)alkyl$; $NH_2-C(=O)-$; $(C_1-C_6)alkyl-NH-C(=O)-$; $[(C_1-C_6)alkyl]_2-N-C(=O)-$; and non-, mono- and di-substituted amino wherein the substituents are independently selected from $(C_1-C_6)alkyl$, $[(C_1-C_6)alkyl]-C(=O)-$, $[(C_1-$

C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-; or

R^{Y6} and R^{Y7} taken together with the nitrogen atom to which they are attached form a four to eight heterocyclyl optionally containing, in addition to the nitrogen atom, one to two additional hetero atoms independently selected from nitrogen, oxygen and sulfur, and said heterocyclyl is optionally substituted with one substituent selected from hydroxy; (C₁-C₆)alkyl; NH₂-C(O=)-; (C₁-C₆)alkyl-NH-C(=O)-; [(C₁-C₆)alkyl]₂-N-C(=O)-; and non-, mono- and di-substituted amino wherein the substituents are independently selected from (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-;

said A is optionally substituted in the fused benzene rings with one to four substituents independently selected from halo; hydroxy; mercapto; phenyl; (C₁-C₆)alkyl optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, [(C₁-C₆)alkyl]-C(=O)-, (C₁-C₆)alkoxy, [(C₁-C₆)alkoxy]-C(=O)-, R^{a1}R^{a2}N- and R^{a3}R^{a4}N-C(=O)-, wherein R^{a1}, R^{a2}, R^{a3} and R^{a4} are independently selected from hydrogen, (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-; and (C₁-C₆)alkoxy optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, [(C₁-C₆)alkyl]-C(=O)-, (C₁-C₆)alkoxy, [(C₁-C₆)alkoxy]-C(=O)-, R^{a5}R^{a6}N- and R^{a7}R^{a8}N-C(=O)-, wherein R^{a5}, R^{a6}, R^{a7} and R^{a8} are independently selected from hydrogen, (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-; and

Z is selected from C(=O); (CH₂)_{n8} wherein n8 is an integer selected from 0, 1 and 2; and CHR^{Z1} wherein

R^{Z1} is selected from carboxy; (C₁-C₆)alkoxy-C(=O)-; non-, mono- and di-substituted amino wherein the substituents are independently selected from (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkyl]-C(=O)-O- and [(C₁-C₆)alkyl]-SO₂-; (C₁-C₆)alkyl optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, [(C₁-C₆)alkyl]-C(=O)-, (C₁-C₆)alkoxy, [(C₁-C₆)alkoxy]-C(=O)-, R^{a1}R^{a2}N- and R^{a3}R^{a4}N-C(=O)-, wherein R^{a1}, R^{a2}, R^{a3} and R^{a4} are independently selected from hydrogen, (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-; and [C(=O)-NR^{Z11}R^{Z12}] wherein R^{Z11} and R^{Z12} are independently selected from hydrogen and

(C₁-C₆)alkyl optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, [(C₁-C₆)alkyl]-C(=O)-, (C₁-C₆)alkoxy, [(C₁-C₆)alkoxy]-C(=O)-, R^{a1}R^{a2}N- and R^{a3}R^{a4}N-C(=O)-, wherein R^{a1}, R^{a2}, R^{a3} and R^{a4} are independently selected from hydrogen, (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-.

4. A compound according to Claim 3 wherein
- all R¹ are hydrogen
- each R² is independently selected from hydrogen and halo;
- 10 X¹ is selected from (CH₂)_{n1} wherein n1 is an integer selected from 1, 2 and 3; O; NH; S; C(=O); SO₂; and N[(C₁-C₄)alkyl];
- X² is selected from CH₂; O; NH; S; C(=O); SO₂; and N[(C₁-C₄)alkyl]; or
- X¹ and X² taken together form CH=CH;
- W¹ and W² are both CH₂;
- 15 A is AB wherein
- Y^b is CR^{Y3}[C(=O)NR^{Y6}R^{Y7}]; and
- Y^c is selected from CR^{Y1}R^{Y2}; CR^{Y3}[C(=O)R^{Y4}]; CR^{Y3}[C(=O)NR^{Y6}R^{Y7}]; and CR^{Y3}[NR^{Y6}R^{Y7}], wherein
- 20 R^{Y1} and R^{Y2} are independently selected from hydrogen; hydroxy; non-, mono- and di-substituted amino wherein the substituents are independently selected from (C₁-C₆)alkyl; [(C₁-C₆)alkyl]-C(=O)-; [(C₁-C₆)alkoxy]-C(=O)-; [(C₁-C₆)alkyl]-SO₂-; and four- to eight-membered heterocyclyl containing one to four hetero atoms independently selected from nitrogen, oxygen and sulfur, wherein said heterocyclyl is optionally substituted with one to three
- 25 substituents independently selected from hydroxy, (C₁-C₆)alkyl, NH₂-C(O=)-, [(C₁-C₆)alkyl]-NH-C(=O)-, [(C₁-C₆)alkyl]₂-N-C(=O)-, and non-, mono- and di-substituted amino wherein the substituents are independently selected from (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-; (C₁-C₆)alkyl optionally substituted with one to three
- 30 substituents independently selected from halo, hydroxy, carboxy, [(C₁-C₆)alkyl]-C(=O)-, (C₁-C₆)alkoxy, [(C₁-C₆)alkoxy]-C(=O)-, R^{a1}R^{a2}N- and R^{a3}R^{a4}N-C(=O)-, wherein R^{a1}, R^{a2}, R^{a3} and R^{a4} are independently selected from

hydrogen, (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-; and (C₁-C₆)alkoxy optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, [(C₁-C₆)alkyl]-C(=O)-, (C₁-C₆)alkoxy, [(C₁-C₆)alkoxy]-C(=O)-, R^{a5}R^{a6}N- and R^{a7}R^{a8}N-C(=O)-, wherein R^{a5}, R^{a6}, R^{a7} and R^{a8} are independently selected from hydrogen, (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-; or

R^{Y1} and R^{Y2} taken together with the carbon atom to which they are attached form spiropyrrolidinyl or spiropiperidinyl, both of which are optionally N-substituted with a substituent selected from (C₁-C₆)alkyl, (C₁-C₆)alkyl-C(=O)-, [(C₁-C₆)alkyl]-C(=O)-(C₁-C₆)alkyl and aryl-(C=O)- wherein aryl is selected from phenyl and naphthyl;

R^{Y3} is hydrogen;

R^{Y4} is selected from hydroxy; (C₁-C₆)alkyl optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, [(C₁-C₆)alkyl]-C(=O)-, (C₁-C₆)alkoxy, [(C₁-C₆)alkoxy]-C(=O)-, R^{a1}R^{a2}N- and R^{a3}R^{a4}N-C(=O)-, wherein R^{a1}, R^{a2}, R^{a3} and R^{a4} are independently selected from hydrogen, (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-; and (C₁-C₆)alkoxy optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, [(C₁-C₆)alkyl]-C(=O)-, (C₁-C₆)alkoxy, [(C₁-C₆)alkoxy]-C(=O)-, R^{a5}R^{a6}N- and R^{a7}R^{a8}N-C(=O)-, wherein R^{a5}, R^{a6}, R^{a7} and R^{a8} are independently selected from hydrogen, (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-; and

R^{Y5}, R^{Y6} and R^{Y7} are independently selected from hydrogen; (C₁-C₆)alkyl optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, [(C₁-C₆)alkyl]-C(=O)-, (C₁-C₆)alkoxy, [(C₁-C₆)alkoxy]-C(=O)-, R^{a1}R^{a2}N- and R^{a3}R^{a4}N-C(=O)-, wherein R^{a1}, R^{a2}, R^{a3} and R^{a4} are independently selected from hydrogen, (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-; heterocyclyl-(CH₂)_{n6}- wherein n₆ is an integer selected from 0, 1, 2, 3 and 4 and said heterocyclyl is four to eight membered containing one to three hetero atoms independently selected

from nitrogen, oxygen and sulfur, wherein said heterocyclyl is optionally substituted with one to three substituents independently selected from hydroxy; (C₁-C₆)alkyl; NH₂-C(O=)-; (C₁-C₆)alkyl-NH-C(=O)-; [(C₁-C₆)alkyl]₂-N-C(=O)-; and non-, mono- and di-substituted amino wherein the substituents are independently selected from (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-; and heteroaryl-(CH₂)_{n7}- wherein n7 is an integer selected from 0, 1, 2, 3 and 4 and said heteroaryl is five to ten membered containing one to three hetero atoms independently selected from nitrogen, oxygen and sulfur, wherein said heteroaryl is optionally substituted with one to three substituents independently selected from hydroxy; (C₁-C₆)alkyl; NH₂-C(O=)-; (C₁-C₆)alkyl-NH-C(=O)-; [(C₁-C₆)alkyl]₂-N-C(=O)-; and non-, mono- and di-substituted amino wherein the substituents are independently selected from (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-; or

R^{Y6} and R^{Y7} taken together with the nitrogen atom to which they are attached form a four to eight heterocyclyl optionally containing, in addition to the nitrogen atom, one to two additional hetero atoms independently selected from nitrogen, oxygen and sulfur, and said heterocyclyl is optionally substituted with one substituent selected from hydroxy; (C₁-C₆)alkyl; NH₂-C(O=)-; (C₁-C₆)alkyl-NH-C(=O)-; [(C₁-C₆)alkyl]₂-N-C(=O)-; and non-, mono- and di-substituted amino wherein the substituents are independently selected from (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-;

said A is optionally substituted in the fused benzene rings with one to four substituents independently selected from halo; hydroxy; mercapto; phenyl; (C₁-C₆)alkyl optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, (C₁-C₆)alkoxy, (C₁-C₆)alkoxy-C(=O)- and non-, mono- and di-substituted amino wherein the substituents are independently selected from (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-; and (C₁-C₆)alkoxy optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, (C₁-C₆)alkoxy, (C₁-C₆)alkoxy-C(=O)- and non-, mono- and di-substituted amino wherein the substituents are independently selected from (C₁-

C_6)alkyl, $[(C_1-C_6)alkyl]-C(=O)-$, $[(C_1-C_6)alkoxy]-C(=O)-$ and $[(C_1-C_6)alkyl]-SO_2-$; and Z is selected from $C(=O)$; $(CH_2)_{n8}$ wherein $n8$ is an integer selected from 0, 1 and 2; and CHR^{Z1} wherein

R^{Z1} is selected from carboxy; $(C_1-C_6)alkoxy-C(=O)-$; non-, mono- and di-substituted amino wherein the substituents are independently selected from $(C_1-C_6)alkyl$, $[(C_1-C_6)alkyl]-C(=O)-$, $[(C_1-C_6)alkyl]-C(=O)-O-$ and $[(C_1-C_6)alkyl]-SO_2-$; $(C_1-C_6)alkyl$ optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, $[(C_1-C_6)alkyl]-C(=O)-$, $(C_1-C_6)alkoxy$, $[(C_1-C_6)alkoxy]-C(=O)-$, $R^{a1}R^{a2}N-$ and $R^{a3}R^{a4}N-C(=O)-$, wherein R^{a1} , R^{a2} , R^{a3} and R^{a4} are independently selected from hydrogen, $(C_1-C_6)alkyl$, $[(C_1-C_6)alkyl]-C(=O)-$, $[(C_1-C_6)alkoxy]-C(=O)-$ and $[(C_1-C_6)alkyl]-SO_2-$; and $[C(=O)-NR^{Z11}R^{Z12}]$ wherein R^{Z11} and R^{Z12} are independently selected from hydrogen and $(C_1-C_6)alkyl$ optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, $[(C_1-C_6)alkyl]-C(=O)-$, $(C_1-C_6)alkoxy$, $[(C_1-C_6)alkoxy]-C(=O)-$, $R^{a1}R^{a2}N-$ and $R^{a3}R^{a4}N-C(=O)-$, wherein R^{a1} , R^{a2} , R^{a3} and R^{a4} are independently selected from hydrogen, $(C_1-C_6)alkyl$, $[(C_1-C_6)alkyl]-C(=O)-$, $[(C_1-C_6)alkoxy]-C(=O)-$ and $[(C_1-C_6)alkyl]-SO_2-$.

5. A compound according to Claim 4 wherein

all R^1 are hydrogen
 each R^2 is independently selected from hydrogen and halo;
 X^1 is selected from $(CH_2)_{n1}$ wherein $n1$ is an integer selected from 1, 2 and 3; O; NH; S; $C(=O)$; SO_2 ; and $N[(C_1-C_4)alkyl]$;
 X^2 is selected from CH_2 ; O; NH; S; $C(=O)$; SO_2 ; and $N[(C_1-C_4)alkyl]$; or
 X^1 and X^2 taken together form $CH=CH$;
 W^1 and W^2 are both CH_2 ;
 A is AB wherein
 Y^b is $CR^{Y3}[C(=O)NR^{Y6}R^{Y7}]$; and
 Y^c is selected from $CR^{Y1}R^{Y2}$; $CR^{Y3}[C(=O)R^{Y4}]$; $CR^{Y3}[C(=O)NR^{Y6}R^{Y7}]$; and
 $CR^{Y3}[NR^{Y6}R^{Y7}]$; wherein
 R^{Y1} and R^{Y2} are independently selected from hydrogen; hydroxy; non-, mono- and di-substituted amino wherein the substituents are independently selected

- from (C₁-C₆)alkyl; [(C₁-C₆)alkyl]-C(=O)-; [(C₁-C₆)alkoxy]-C(=O)-; [(C₁-C₆)alkyl]-SO₂-; and four- to eight-membered heterocyclyl containing one to four hetero atoms independently selected from nitrogen, oxygen and sulfur, wherein said heterocyclyl is optionally substituted with one to three substituents independently selected from hydroxy, (C₁-C₆)alkyl, NH₂-C(O=)-, [(C₁-C₆)alkyl]-NH-C(=O)-, [(C₁-C₆)alkyl]₂-N-C(=O)-, and non-, mono- and di-substituted amino wherein the substituents are independently selected from (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-; (C₁-C₆)alkyl optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, [(C₁-C₆)alkyl]-C(=O)-, (C₁-C₆)alkoxy, [(C₁-C₆)alkoxy]-C(=O)-, R^{a1}R^{a2}N- and R^{a3}R^{a4}N-C(=O)-, wherein R^{a1}, R^{a2}, R^{a3} and R^{a4} are independently selected from hydrogen, (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-; and (C₁-C₆)alkoxy optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, [(C₁-C₆)alkyl]-C(=O)-, (C₁-C₆)alkoxy, [(C₁-C₆)alkoxy]-C(=O)-, R^{a5}R^{a6}N- and R^{a7}R^{a8}N-C(=O)-, wherein R^{a5}, R^{a6}, R^{a7} and R^{a8} are independently selected from hydrogen, (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-; or
- R^{Y1} and R^{Y2} taken together with the carbon atom to which they are attached form spiropyrrolidinyl or spiropiperidinyl, both of which are optionally N-substituted with a substituent selected from (C₁-C₆)alkyl, (C₁-C₆)alkyl-C(=O)-, [(C₁-C₆)alkyl]-C(=O)-(C₁-C₆)alkyl and aryl-(C=O)- wherein aryl is selected from phenyl and naphthyl;
- R^{Y3} is hydrogen;
- R^{Y4} is selected from hydroxy; (C₁-C₆)alkyl optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, [(C₁-C₆)alkyl]-C(=O)-, (C₁-C₆)alkoxy, [(C₁-C₆)alkoxy]-C(=O)-, R^{a1}R^{a2}N- and R^{a3}R^{a4}N-C(=O)-, wherein R^{a1}, R^{a2}, R^{a3} and R^{a4} are independently selected from hydrogen, (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-; and (C₁-C₆)alkoxy optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, [(C₁-

C₆)alkyl]-C(=O)-, (C₁-C₆)alkoxy, [(C₁-C₆)alkoxy]-C(=O)-, R^{a5}R^{a6}N- and R^{a7}R^{a8}N-C(=O)-, wherein R^{a5}, R^{a6}, R^{a7} and R^{a8} are independently selected from hydrogen, (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-; and

5 R^{Y5}, R^{Y6} and R^{Y7} are independently selected from hydrogen; (C₁-C₆)alkyl optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, [(C₁-C₆)alkyl]-C(=O)-, (C₁-C₆)alkoxy, [(C₁-C₆)alkoxy]-C(=O)-, R^{a1}R^{a2}N- and R^{a3}R^{a4}N-C(=O)-, wherein R^{a1}, R^{a2}, R^{a3} and R^{a4} are independently selected from hydrogen, (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, 10 [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-; heterocyclyl-(CH₂)_{n6}- wherein n₆ is an integer selected from 0, 1, 2, 3 and 4 and said heterocyclyl is four to eight membered containing one to three hetero atoms independently selected from nitrogen, oxygen and sulfur, wherein said heterocyclyl is optionally substituted with one to three substituents independently selected from hydroxy; 15 (C₁-C₆)alkyl; NH₂-C(=O)-; (C₁-C₆)alkyl-NH-C(=O)-; [(C₁-C₆)alkyl]₂-N-C(=O)-; and non-, mono- and di-substituted amino wherein the substituents are independently selected from (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-; and heteroaryl-(CH₂)_{n7}- wherein n₇ is an integer selected from 0, 1, 2, 3 and 4 and said heteroaryl is five to ten 20 membered containing one to three hetero atoms independently selected from nitrogen, oxygen and sulfur, wherein said heteroaryl is optionally substituted with one to three substituents independently selected from hydroxy; (C₁-C₆)alkyl; NH₂-C(=O)-; (C₁-C₆)alkyl-NH-C(=O)-; [(C₁-C₆)alkyl]₂-N-C(=O)-; and non-, mono- and di-substituted amino wherein the substituents are 25 independently selected from (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-; or

R^{Y6} and R^{Y7} taken together with the nitrogen atom to which they are attached form a four to eight heterocyclyl optionally containing, in addition to the nitrogen atom, one to two additional hetero atoms independently selected 30 from nitrogen, oxygen and sulfur, and said heterocyclyl is optionally substituted with one substituent selected from hydroxy; (C₁-C₆)alkyl; NH₂-C(=O)-; (C₁-C₆)alkyl-NH-C(=O)-; [(C₁-C₆)alkyl]₂-N-C(=O)-; and non-,

mono- and di-substituted amino wherein the substituents are independently selected from (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-;

said A is optionally substituted in the fused benzene rings with one to four substituents independently selected from halo; hydroxy; mercapto; phenyl; (C₁-C₆)alkyl optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, (C₁-C₆)alkoxy, (C₁-C₆)alkoxy-C(=O)- and non-, mono- and di-substituted amino wherein the substituents are independently selected from (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-; and (C₁-C₆)alkoxy optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, (C₁-C₆)alkoxy, (C₁-C₆)alkoxy-C(=O)- and non-, mono- and di-substituted amino wherein the substituents are independently selected from (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-; and Z is C(=O).

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6. A compound according to Claim 3 wherein
all R¹ are hydrogen
each R² is independently selected from hydrogen and halo;
X¹ is selected from (CH₂)_{n1} wherein n1 is an integer selected from 1, 2 and 3; O; NH;
S; C(=O); SO₂; and N[(C₁-C₄)alkyl];
X² is selected from CH₂; O; NH; S; C(=O); SO₂; and N[(C₁-C₄)alkyl]; or
X¹ and X² taken together form CH=CH;
W¹ and W² are both CH₂;
A is AB wherein

25 Y^b is CR^{Y1}R^{Y2}; and
Y^c is selected from CR^{Y1}R^{Y2}; CR^{Y3}[C(=O)R^{Y4}]; CR^{Y3}[C(=O)NR^{Y6}R^{Y7}]; and
CR^{Y3}[NR^{Y6}R^{Y7}]; or

Y^b and Y^c taken together form a group selected from CH₂-CH₂ and CH₂=CH₂;
R^{Y1} and R^{Y2} are independently selected from hydrogen; hydroxy; non-, mono-
and di-substituted amino wherein the substituents are independently selected
30 from (C₁-C₆)alkyl; [(C₁-C₆)alkyl]-C(=O)-; [(C₁-C₆)alkoxy]-C(=O)-; [(C₁-C₆)alkyl]-SO₂-; and four- to eight-membered heterocyclyl containing one to

four hetero atoms independently selected from nitrogen, oxygen and sulfur, wherein said heterocyclyl is optionally substituted with one to three substituents independently selected from hydroxy, (C₁-C₆)alkyl, NH₂-C(=O)-, [(C₁-C₆)alkyl]-NH-C(=O)-, [(C₁-C₆)alkyl]₂-N-C(=O)-, and non-, mono- and di-substituted amino wherein the substituents are independently selected from (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-; (C₁-C₆)alkyl optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, [(C₁-C₆)alkyl]-C(=O)-, (C₁-C₆)alkoxy, [(C₁-C₆)alkoxy]-C(=O)-, R^{a1}R^{a2}N- and R^{a3}R^{a4}N-C(=O)-, wherein R^{a1}, R^{a2}, R^{a3} and R^{a4} are independently selected from hydrogen, (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-; and (C₁-C₆)alkoxy optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, [(C₁-C₆)alkyl]-C(=O)-, (C₁-C₆)alkoxy, [(C₁-C₆)alkoxy]-C(=O)-, R^{a5}R^{a6}N- and R^{a7}R^{a8}N-C(=O)-, wherein R^{a5}, R^{a6}, R^{a7} and R^{a8} are independently selected from hydrogen, (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-; or

R^{Y1} and R^{Y2} taken together with the carbon atom to which they are attached form spiropyrrolidinyl or spiropiperidinyl, both of which are optionally N-substituted with a substituent selected from (C₁-C₆)alkyl, (C₁-C₆)alkyl-C(=O)-, [(C₁-C₆)alkyl]-C(=O)-(C₁-C₆)alkyl and aryl-(C=O)- wherein aryl is selected from phenyl and naphthyl;

R^{Y3} is hydrogen;

R^{Y4} is selected from hydroxy; (C₁-C₆)alkyl optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, [(C₁-C₆)alkyl]-C(=O)-, (C₁-C₆)alkoxy, [(C₁-C₆)alkoxy]-C(=O)-, R^{a1}R^{a2}N- and R^{a3}R^{a4}N-C(=O)-, wherein R^{a1}, R^{a2}, R^{a3} and R^{a4} are independently selected from hydrogen, (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-; and (C₁-C₆)alkoxy optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, [(C₁-C₆)alkyl]-C(=O)-, (C₁-C₆)alkoxy, [(C₁-C₆)alkoxy]-C(=O)-, R^{a5}R^{a6}N- and R^{a7}R^{a8}N-C(=O)-, wherein R^{a5}, R^{a6}, R^{a7} and R^{a8} are independently selected from

hydrogen, (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-; and

R^{Y6} and R^{Y7} are independently selected from hydrogen; (C₁-C₆)alkyl optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, [(C₁-C₆)alkyl]-C(=O)-, (C₁-C₆)alkoxy, [(C₁-C₆)alkoxy]-C(=O)-, R^{a1}R^{a2}N- and R^{a3}R^{a4}N-C(=O)-, wherein R^{a1}, R^{a2}, R^{a3} and R^{a4} are independently selected from hydrogen, (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-; heterocyclyl-(CH₂)_{n6}- wherein n₆ is an integer selected from 0, 1, 2, 3 and 4 and said heterocyclyl is four to eight membered containing one to three hetero atoms independently selected from nitrogen, oxygen and sulfur, wherein said heterocyclyl is optionally substituted with one to three substituents independently selected from hydroxy; (C₁-C₆)alkyl; NH₂-C(O=)-; (C₁-C₆)alkyl-NH-C(=O)-; [(C₁-C₆)alkyl]₂-N-C(=O)-; and non-, mono- and di-substituted amino wherein the substituents are independently selected from (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-; and heteroaryl-(CH₂)_{n7}- wherein n₇ is an integer selected from 0, 1, 2, 3 and 4 and said heteroaryl is five to ten membered containing one to three hetero atoms independently selected from nitrogen, oxygen and sulfur, wherein said heteroaryl is optionally substituted with one to three substituents independently selected from hydroxy; (C₁-C₆)alkyl; NH₂-C(O=)-; (C₁-C₆)alkyl-NH-C(=O)-; [(C₁-C₆)alkyl]₂-N-C(=O)-; and non-, mono- and di-substituted amino wherein the substituents are independently selected from (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-; or

R^{Y6} and R^{Y7} taken together with the nitrogen atom to which they are attached form a four to eight heterocyclyl optionally containing, in addition to the nitrogen atom, one to two additional hetero atoms independently selected from nitrogen, oxygen and sulfur, and said heterocyclyl is optionally substituted with one substituent selected from hydroxy; (C₁-C₆)alkyl; NH₂-C(O=)-; (C₁-C₆)alkyl-NH-C(=O)-; [(C₁-C₆)alkyl]₂-N-C(=O)-; and non-, mono- and di-substituted amino wherein the substituents are independently selected from (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)-

and [(C₁-C₆)alkyl]-SO₂-;

said A is optionally substituted in the fused benzene rings with one to four substituents independently selected from halo; hydroxy; mercapto; phenyl; (C₁-C₆)alkyl optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, [(C₁-C₆)alkyl]-C(=O)-, (C₁-C₆)alkoxy, [(C₁-C₆)alkoxy]-C(=O)-, R^{a1}R^{a2}N- and R^{a3}R^{a4}N-C(=O)-, wherein R^{a1}, R^{a2}, R^{a3} and R^{a4} are independently selected from hydrogen, (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-; and (C₁-C₆)alkoxy optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, [(C₁-C₆)alkyl]-C(=O)-, (C₁-C₆)alkoxy, [(C₁-C₆)alkoxy]-C(=O)-, R^{a5}R^{a6}N- and R^{a7}R^{a8}N-C(=O)-, wherein R^{a5}, R^{a6}, R^{a7} and R^{a8} are independently selected from hydrogen, (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-; and Z is C(=O).

7. A compound according to Claim 2 wherein

all R¹ are hydrogen

each R² is independently selected from hydrogen and halo;

X¹ is selected from (CH₂)_{n1} wherein n1 is an integer selected from 1, 2 and 3; O; NH; S; C(=O); SO₂; and N[(C₁-C₄)alkyl];

X² is selected from CH₂; O; NH; S; C(=O); SO₂; and N[(C₁-C₄)alkyl]; or

X¹ and X² taken together form CH=CH;

W¹ and W² are both CH₂;

A is AB wherein

Y^b is selected from C(=O); CR^{Y1}R^{Y2}; CR^{Y3}[C(=O)R^{Y4}]; CR^{Y3}[NR^{Y5}C(=O)R^{Y4}];

CR^{Y3}[C(=O)NR^{Y6}R^{Y7}]; and CR^{Y3}[NR^{Y6}R^{Y7}];

Y^c is selected from O; S; SO₂; NH; N[(C₁-C₆)alkyl] wherein said (C₁-C₆)alkyl is optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, [(C₁-C₆)alkyl]-C(=O)-, (C₁-C₆)alkoxy, [(C₁-C₆)alkoxy]-C(=O)-, R^{a1}R^{a2}N- and R^{a3}R^{a4}N-C(=O)-, wherein R^{a1}, R^{a2}, R^{a3} and R^{a4} are independently selected from hydrogen, (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-; N-(CH₂)_{n3}-heterocyclyl wherein n3 is an integer selected from 0, 1, 2 and 3, and said heterocyclyl contains from four to eight ring atoms one or two of

which are independently selected from nitrogen, oxygen and sulfur; $N-(CH_2)_{n4}$ -aryl wherein $n4$ is an integer selected from 0, 1, 2 and 3, and said aryl is selected from phenyl and naphthyl; and $N-(CH_2)_{n5}$ -heteroaryl wherein $n5$ is an integer selected from 0, 1, 2 and 3, and said heteroaryl is a five to ten membered aromatic heterocyclyl
 5 containing from one to four hetero atoms independently selected from nitrogen, oxygen and sulfur; wherein

R^{Y1} and R^{Y2} are independently selected from hydrogen; hydroxy; non-, mono- and di-substituted amino wherein the substituents are independently selected from (C_1-C_6) alkyl; $[(C_1-C_6)alkyl]-C(=O)-$; $[(C_1-C_6)alkoxy]-C(=O)-$; $[(C_1-C_6)alkyl]-SO_2-$; and four- to eight-membered heterocyclyl containing one to
 10 four hetero atoms independently selected from nitrogen, oxygen and sulfur, wherein said heterocyclyl is optionally substituted with one to three substituents independently selected from hydroxy, (C_1-C_6) alkyl, $NH_2-C(=O)-$, $[(C_1-C_6)alkyl]-NH-C(=O)-$, $[(C_1-C_6)alkyl]_2-N-C(=O)-$, and non-, mono- and di-substituted amino wherein the substituents are independently selected from
 15 (C_1-C_6) alkyl, $[(C_1-C_6)alkyl]-C(=O)-$, $[(C_1-C_6)alkoxy]-C(=O)-$ and $[(C_1-C_6)alkyl]-SO_2-$; (C_1-C_6) alkyl optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, $[(C_1-C_6)alkyl]-C(=O)-$, $(C_1-C_6)alkoxy$, $[(C_1-C_6)alkoxy]-C(=O)-$, $R^{a1}R^{a2}N-$ and
 20 $R^{a3}R^{a4}N-C(=O)-$, wherein R^{a1} , R^{a2} , R^{a3} and R^{a4} are independently selected from hydrogen, (C_1-C_6) alkyl, $[(C_1-C_6)alkyl]-C(=O)-$, $[(C_1-C_6)alkoxy]-C(=O)-$ and $[(C_1-C_6)alkyl]-SO_2-$; and $(C_1-C_6)alkoxy$ optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, $[(C_1-C_6)alkyl]-C(=O)-$, $(C_1-C_6)alkoxy$, $[(C_1-C_6)alkoxy]-C(=O)-$, $R^{a5}R^{a6}N-$ and
 25 $R^{a7}R^{a8}N-C(=O)-$, wherein R^{a5} , R^{a6} , R^{a7} and R^{a8} are independently selected from hydrogen, (C_1-C_6) alkyl, $[(C_1-C_6)alkyl]-C(=O)-$, $[(C_1-C_6)alkoxy]-C(=O)-$ and $[(C_1-C_6)alkyl]-SO_2-$; or

R^{Y1} and R^{Y2} taken together with the carbon atom to which they are attached form spiropyrrolidinyll or spiropiperidinyll, both of which are optionally N-substituted with a substituent selected from (C_1-C_6) alkyl, $(C_1-C_6)alkyl-C(=O)-$, $[(C_1-C_6)alkyl]-C(=O)-(C_1-C_6)alkyl$ and aryl- $C(=O)-$ wherein aryl is
 30 selected from phenyl and naphthyl;

R^{Y3} is hydrogen;

R^{Y4} is selected from hydroxy; (C_1-C_6) alkyl optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, $[(C_1-C_6)alkyl]-C(=O)-$, $(C_1-C_6)alkoxy$, $[(C_1-C_6)alkoxy]-C(=O)-$, $R^{a1}R^{a2}N-$ and $R^{a3}R^{a4}N-C(=O)-$, wherein R^{a1} , R^{a2} , R^{a3} and R^{a4} are independently selected from hydrogen, $(C_1-C_6)alkyl$, $[(C_1-C_6)alkyl]-C(=O)-$, $[(C_1-C_6)alkoxy]-C(=O)-$ and $[(C_1-C_6)alkyl]-SO_2-$; and $(C_1-C_6)alkoxy$ optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, $[(C_1-C_6)alkyl]-C(=O)-$, $(C_1-C_6)alkoxy$, $[(C_1-C_6)alkoxy]-C(=O)-$, $R^{a5}R^{a6}N-$ and $R^{a7}R^{a8}N-C(=O)-$, wherein R^{a5} , R^{a6} , R^{a7} and R^{a8} are independently selected from hydrogen, $(C_1-C_6)alkyl$, $[(C_1-C_6)alkyl]-C(=O)-$, $[(C_1-C_6)alkoxy]-C(=O)-$ and $[(C_1-C_6)alkyl]-SO_2-$; and

R^{Y5} , R^{Y6} and R^{Y7} are independently selected from hydrogen; $(C_1-C_6)alkyl$ optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, $[(C_1-C_6)alkyl]-C(=O)-$, $(C_1-C_6)alkoxy$, $[(C_1-C_6)alkoxy]-C(=O)-$, $R^{a1}R^{a2}N-$ and $R^{a3}R^{a4}N-C(=O)-$, wherein R^{a1} , R^{a2} , R^{a3} and R^{a4} are independently selected from hydrogen, $(C_1-C_6)alkyl$, $[(C_1-C_6)alkyl]-C(=O)-$, $[(C_1-C_6)alkoxy]-C(=O)-$ and $[(C_1-C_6)alkyl]-SO_2-$; heterocyclyl- $(CH_2)_{n6}-$ wherein $n6$ is an integer selected from 0, 1, 2, 3 and 4 and said heterocyclyl is four to eight membered containing one to three hetero atoms independently selected from nitrogen, oxygen and sulfur, wherein said heterocyclyl is optionally substituted with one to three substituents independently selected from hydroxy; $(C_1-C_6)alkyl$; $NH_2-C(=O)-$; $(C_1-C_6)alkyl-NH-C(=O)-$; $[(C_1-C_6)alkyl]_2-N-C(=O)-$; and non-, mono- and di-substituted amino wherein the substituents are independently selected from $(C_1-C_6)alkyl$, $[(C_1-C_6)alkyl]-C(=O)-$, $[(C_1-C_6)alkoxy]-C(=O)-$ and $[(C_1-C_6)alkyl]-SO_2-$; and

heteroaryl- $(CH_2)_{n7}-$ wherein $n7$ is an integer selected from 0, 1, 2, 3 and 4 and said heteroaryl is five to ten membered containing one to three hetero atoms independently selected from nitrogen, oxygen and sulfur, wherein said heteroaryl is optionally substituted with one to three substituents independently selected from hydroxy; $(C_1-C_6)alkyl$; $NH_2-C(=O)-$; $(C_1-C_6)alkyl-NH-C(=O)-$; $[(C_1-C_6)alkyl]_2-N-C(=O)-$; and non-, mono- and di-

substituted amino wherein the substituents are independently selected from (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-; or

5 R^{Y6} and R^{Y7} taken together with the nitrogen atom to which they are attached form a four to eight heterocyclyl optionally containing, in addition to the nitrogen atom, one to two additional hetero atoms independently selected from nitrogen, oxygen and sulfur, and said heterocyclyl is optionally substituted with one substituent selected from hydroxy; (C₁-C₆)alkyl; NH₂-C(O=)-; (C₁-C₆)alkyl-NH-C(=O)-; [(C₁-C₆)alkyl]₂-N-C(=O)-; and non-,
10 mono- and di-substituted amino wherein the substituents are independently selected from (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-;

said A is optionally substituted in the fused benzene rings with one to four substituents independently selected from halo; hydroxy; mercapto; phenyl; (C₁-C₆)alkyl optionally
15 substituted with one to three substituents independently selected from halo, hydroxy, carboxy, [(C₁-C₆)alkyl]-C(=O)-, (C₁-C₆)alkoxy, [(C₁-C₆)alkoxy]-C(=O)-, R^{a1}R^{a2}N- and R^{a3}R^{a4}N-C(=O)-, wherein R^{a1}, R^{a2}, R^{a3} and R^{a4} are independently selected from hydrogen, (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-; and (C₁-C₆)alkoxy optionally substituted with one to three substituents
20 independently selected from halo, hydroxy, carboxy, [(C₁-C₆)alkyl]-C(=O)-, (C₁-C₆)alkoxy, [(C₁-C₆)alkoxy]-C(=O)-, R^{a5}R^{a6}N- and R^{a7}R^{a8}N-C(=O)-, wherein R^{a5}, R^{a6}, R^{a7} and R^{a8} are independently selected from hydrogen, (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-; and

Z is selected from C(=O); (CH₂)_{n8} wherein n8 is an integer selected from 0, 1 and 2;
25 and CHR^{Z1} wherein

R^{Z1} is selected from carboxy; (C₁-C₆)alkoxy-C(=O)-; non-, mono- and di-substituted amino wherein the substituents are independently selected from (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkyl]-C(=O)-O- and [(C₁-C₆)alkyl]-SO₂-; (C₁-C₆)alkyl optionally substituted with one to three substituents
30 independently selected from halo, hydroxy, carboxy, [(C₁-C₆)alkyl]-C(=O)-, (C₁-C₆)alkoxy, [(C₁-C₆)alkoxy]-C(=O)-, R^{a1}R^{a2}N- and R^{a3}R^{a4}N-C(=O)-, wherein R^{a1}, R^{a2}, R^{a3} and R^{a4} are independently selected from hydrogen, (C₁-C₆)alkyl, [(C₁-

C_6)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-; and
 [C(=O)-NR^{Z11}R^{Z12}] wherein R^{Z11} and R^{Z12} are independently selected from
 hydrogen and (C₁-C₆)alkyl optionally substituted with one to three substituents
 independently selected from halo, hydroxy, carboxy, [(C₁-C₆)alkyl]-C(=O)-, (C₁-
 5 C₆)alkoxy, [(C₁-C₆)alkoxy]-C(=O)-, R^{a1}R^{a2}N- and R^{a3}R^{a4}N-C(=O)-, wherein R^{a1},
 R^{a2}, R^{a3} and R^{a4} are independently selected from hydrogen, (C₁-C₆)alkyl, [(C₁-
 C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-.

8. A compound according to Claim 1 wherein
 10 all R¹ are hydrogen
 each R² is independently selected from hydrogen and halo;
 X¹ is selected from (CH₂)_{n1} wherein n1 is an integer selected from 1, 2 and 3; O; NH;
 S; C(=O); SO₂; and N[(C₁-C₄)alkyl];
 X² is selected from CH₂; O; NH; S; C(=O); SO₂; and N[(C₁-C₄)alkyl]; or
 15 X¹ and X² taken together form CH=CH;
 W¹ and W² are independently selected from CR^{W1}R^{W2},
 wherein
 R^{W1} and R^{W2} are independently selected from hydrogen; halo; hydroxy; (C₁-
 C₆)alkyl optionally substituted with one to three substituents independently
 20 selected from halo, hydroxy, carboxy, [(C₁-C₆)alkyl]-C(=O)-, (C₁-C₆)alkoxy, [(C₁-
 C₆)alkoxy]-C(=O)-, R^{a1}R^{a2}N- and R^{a3}R^{a4}N-C(=O)-, wherein R^{a1}, R^{a2}, R^{a3} and R^{a4}
 are independently selected from hydrogen, (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-,
 [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-; (C₁-C₆)alkoxy optionally
 substituted with one to three substituents independently selected from halo,
 25 hydroxy, carboxy, [(C₁-C₆)alkyl]-C(=O)-, (C₁-C₆)alkoxy, [(C₁-C₆)alkoxy]-C(=O)-,
 R^{a5}R^{a6}N- and R^{a7}R^{a8}N-C(=O)-, wherein R^{a5}, R^{a6}, R^{a7} and R^{a8} are independently
 selected from hydrogen, (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-
 C(=O)- and [(C₁-C₆)alkyl]-SO₂-; C(=O)-[(C₁-C₆)alkyl] wherein said (C₁-C₆)alkyl
 is optionally substituted with one to three substituents independently selected from
 30 halo, hydroxy, carboxy, [(C₁-C₆)alkyl]-C(=O)-, (C₁-C₆)alkoxy, [(C₁-C₆)alkoxy]-
 C(=O)-, R^{a1}R^{a2}N- and R^{a3}R^{a4}N-C(=O)-, wherein R^{a1}, R^{a2}, R^{a3} and R^{a4} are
 independently selected from hydrogen, (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-

C_6)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-; C(=O)-NR^{W11}R^{W12} wherein R^{W11} and R^{W12} are independently selected from hydrogen and (C₁-C₆)alkyl optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, [(C₁-C₆)alkyl]-C(=O)-, (C₁-C₆)alkoxy, [(C₁-C₆)alkoxy]-C(=O)-, R^{a1}R^{a2}N- and R^{a3}R^{a4}N-C(=O)-, wherein R^{a1}, R^{a2}, R^{a3} and R^{a4} are independently selected from hydrogen, (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-; NR^{W13}R^{W14} wherein R^{W13} and R^{W14} are independently selected from hydrogen and (C₁-C₆)alkyl optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, [(C₁-C₆)alkyl]-C(=O)-, (C₁-C₆)alkoxy, [(C₁-C₆)alkoxy]-C(=O)-, R^{a1}R^{a2}N- and R^{a3}R^{a4}N-C(=O)-, wherein R^{a1}, R^{a2}, R^{a3} and R^{a4} are independently selected from hydrogen, (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-; aryl selected from phenyl and naphthyl; and four- to eight-membered heterocyclyl containing one to four hetero atoms independently selected from nitrogen, oxygen and sulfur;

A is AC wherein

Y^d, Y^e and Y^f are independently selected from C(=O); CR^{Y1}R^{Y2}; CR^{Y3}[C(=O)R^{Y4}]; CR^{Y3}[NR^{Y5}C(=O)R^{Y4}]; CR^{Y3}[C(=O)NR^{Y6}R^{Y7}]; CR^{Y3}[NR^{Y6}R^{Y7}]; O; S; SO₂; NH; N[(C₁-C₆)alkyl] wherein said (C₁-C₆)alkyl is optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, [(C₁-C₆)alkyl]-C(=O)-, (C₁-C₆)alkoxy, [(C₁-C₆)alkoxy]-C(=O)-, R^{a1}R^{a2}N- and R^{a3}R^{a4}N-C(=O)-, wherein R^{a1}, R^{a2}, R^{a3} and R^{a4} are independently selected from hydrogen, (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-; N-(CH₂)_{n3}-heterocyclyl wherein n3 is an integer selected from 0, 1, 2 and 3, and said heterocyclyl contains from four to eight ring atoms one or two of which are independently selected from nitrogen, oxygen and sulfur; N-(CH₂)_{n4}-aryl wherein n4 is an integer selected from 0, 1, 2 and 3, and said aryl is selected from phenyl and naphthyl; and N-(CH₂)_{n5}-heteroaryl wherein n5 is an integer selected from 0, 1, 2 and 3, and said heteroaryl is a five to ten membered aromatic heterocyclyl containing from one to four hetero atoms independently selected from nitrogen, oxygen and sulfur;

R^{Y1} and R^{Y2} are independently selected from hydrogen; hydroxy; non-, mono-

and di-substituted amino wherein the substituents are independently selected from (C₁-C₆)alkyl; [(C₁-C₆)alkyl]-C(=O)-; [(C₁-C₆)alkoxy]-C(=O)-; [(C₁-C₆)alkyl]-SO₂-; and four- to eight-membered heterocyclyl containing one to four hetero atoms independently selected from nitrogen, oxygen and sulfur, wherein said heterocyclyl is optionally substituted with one to three substituents independently selected from hydroxy, (C₁-C₆)alkyl, NH₂-C(O=)-, [(C₁-C₆)alkyl]-NH-C(=O)-, [(C₁-C₆)alkyl]₂-N-C(=O)-, and non-, mono- and di-substituted amino wherein the substituents are independently selected from (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-; (C₁-C₆)alkyl optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, [(C₁-C₆)alkyl]-C(=O)-, (C₁-C₆)alkoxy, [(C₁-C₆)alkoxy]-C(=O)-, R^{a1}R^{a2}N- and R^{a3}R^{a4}N-C(=O)-, wherein R^{a1}, R^{a2}, R^{a3} and R^{a4} are independently selected from hydrogen, (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-; and (C₁-C₆)alkoxy optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, [(C₁-C₆)alkyl]-C(=O)-, (C₁-C₆)alkoxy, [(C₁-C₆)alkoxy]-C(=O)-, R^{a5}R^{a6}N- and R^{a7}R^{a8}N-C(=O)-, wherein R^{a5}, R^{a6}, R^{a7} and R^{a8} are independently selected from hydrogen, (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-; or

R^{Y1} and R^{Y2} taken together with the carbon atom to which they are attached form spiropyrrolidinyl or spiropiperidinyl, both of which are optionally N-substituted with a substituent selected from (C₁-C₆)alkyl, (C₁-C₆)alkyl-C(=O)-, [(C₁-C₆)alkyl]-C(=O)-(C₁-C₆)alkyl and aryl-(C=O)- wherein aryl is selected from phenyl and naphthyl;

R^{Y3} is hydrogen;

R^{Y4} is selected from hydroxy; (C₁-C₆)alkyl optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, [(C₁-C₆)alkyl]-C(=O)-, (C₁-C₆)alkoxy, [(C₁-C₆)alkoxy]-C(=O)-, R^{a1}R^{a2}N- and R^{a3}R^{a4}N-C(=O)-, wherein R^{a1}, R^{a2}, R^{a3} and R^{a4} are independently selected from hydrogen, (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-; and (C₁-C₆)alkoxy optionally substituted with one to three

substituents independently selected from halo, hydroxy, carboxy, [(C₁-C₆)alkyl]-C(=O)-, (C₁-C₆)alkoxy, [(C₁-C₆)alkoxy]-C(=O)-, R^{a5}R^{a6}N- and R^{a7}R^{a8}N-C(=O)-, wherein R^{a5}, R^{a6}, R^{a7} and R^{a8} are independently selected from hydrogen, (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-; and

R^{Y5}, R^{Y6} and R^{Y7} are independently selected from hydrogen; (C₁-C₆)alkyl optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, [(C₁-C₆)alkyl]-C(=O)-, (C₁-C₆)alkoxy, [(C₁-C₆)alkoxy]-C(=O)-, R^{a1}R^{a2}N- and R^{a3}R^{a4}N-C(=O)-, wherein R^{a1}, R^{a2}, R^{a3} and R^{a4} are independently selected from hydrogen, (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-; heterocyclyl-(CH₂)_{n6}- wherein n₆ is an integer selected from 0, 1, 2, 3 and 4 and said heterocyclyl is four to eight membered containing one to three hetero atoms independently selected from nitrogen, oxygen and sulfur, wherein said heterocyclyl is optionally substituted with one to three substituents independently selected from hydroxy; (C₁-C₆)alkyl; NH₂-C(=O)-; (C₁-C₆)alkyl-NH-C(=O)-; [(C₁-C₆)alkyl]₂-N-C(=O)-; and non-, mono- and di-substituted amino wherein the substituents are independently selected from (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-; and heteroaryl-(CH₂)_{n7}- wherein n₇ is an integer selected from 0, 1, 2, 3 and 4 and said heteroaryl is five to ten membered containing one to three hetero atoms independently selected from nitrogen, oxygen and sulfur, wherein said heteroaryl is optionally substituted with one to three substituents independently selected from hydroxy; (C₁-C₆)alkyl; NH₂-C(=O)-; (C₁-C₆)alkyl-NH-C(=O)-; [(C₁-C₆)alkyl]₂-N-C(=O)-; and non-, mono- and di-substituted amino wherein the substituents are independently selected from (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-; or

R^{Y6} and R^{Y7} taken together with the nitrogen atom to which they are attached form a four to eight heterocyclyl optionally containing, in addition to the nitrogen atom, one to two additional hetero atoms independently selected from nitrogen, oxygen and sulfur, and said heterocyclyl is optionally substituted with one substituent selected from hydroxy; (C₁-C₆)alkyl; NH₂-

C(O=)-; (C₁-C₆)alkyl-NH-C(=O)-; [(C₁-C₆)alkyl]₂-N-C(=O)-; and non-, mono- and di-substituted amino wherein the substituents are independently selected from (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-; and

5 said A is optionally substituted in the fused benzene rings with one to four substituents independently selected from halo; hydroxy; mercapto; phenyl; (C₁-C₆)alkyl optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, [(C₁-C₆)alkyl]-C(=O)-, (C₁-C₆)alkoxy, [(C₁-C₆)alkoxy]-C(=O)-, R^{a1}R^{a2}N- and R^{a3}R^{a4}N-C(=O)-, wherein R^{a1}, R^{a2}, R^{a3} and R^{a4} are independently selected from
 10 hydrogen, (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-; and (C₁-C₆)alkoxy optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, [(C₁-C₆)alkyl]-C(=O)-, (C₁-C₆)alkoxy, [(C₁-C₆)alkoxy]-C(=O)-, R^{a5}R^{a6}N- and R^{a7}R^{a8}N-C(=O)-, wherein R^{a5}, R^{a6}, R^{a7} and R^{a8} are independently selected from hydrogen, (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-
 15 C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-; and

Z is selected from C(=O); (CH₂)_{n8} wherein n8 is an integer selected from 0, 1 and 2; and CHR^{Z1} wherein

R^{Z1} is selected from carboxy; (C₁-C₆)alkoxy-C(=O)-; non-, mono- and di-substituted amino wherein the substituents are independently selected from (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkyl]-C(=O)-O- and [(C₁-C₆)alkyl]-
 20 SO₂-; (C₁-C₆)alkyl optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, [(C₁-C₆)alkyl]-C(=O)-, (C₁-C₆)alkoxy, [(C₁-C₆)alkoxy]-C(=O)-, R^{a1}R^{a2}N- and R^{a3}R^{a4}N-C(=O)-, wherein R^{a1}, R^{a2}, R^{a3} and R^{a4} are independently selected from hydrogen, (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-; and
 25 [C(=O)-NR^{Z11}R^{Z12}] wherein R^{Z11} and R^{Z12} are independently selected from hydrogen and (C₁-C₆)alkyl optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, [(C₁-C₆)alkyl]-C(=O)-, (C₁-C₆)alkoxy, [(C₁-C₆)alkoxy]-C(=O)-, R^{a1}R^{a2}N- and R^{a3}R^{a4}N-C(=O)-, wherein R^{a1}, R^{a2}, R^{a3} and R^{a4} are independently selected from hydrogen, (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-.
 30

9. A compound according to Claim 1 wherein

all R^1 are hydrogen

each R^2 is independently selected from hydrogen and halo;

X^1 is selected from $(CH_2)_{n1}$ wherein $n1$ is an integer selected from 1, 2 and 3; O; NH;

5 S; C(=O); SO₂; and N[(C₁-C₄)alkyl];

X^2 is selected from CH₂; O; NH; S; C(=O); SO₂; and N[(C₁-C₄)alkyl]; or

X^1 and X^2 taken together form CH=CH;

W^1 and W^2 are independently selected from CR^{W1}R^{W2},

wherein

10 R^{W1} and R^{W2} are independently selected from hydrogen; halo; hydroxy; (C₁-C₆)alkyl optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, [(C₁-C₆)alkyl]-C(=O)-, (C₁-C₆)alkoxy, [(C₁-C₆)alkoxy]-C(=O)-, R^{a1}R^{a2}N- and R^{a3}R^{a4}N-C(=O)-, wherein R^{a1}, R^{a2}, R^{a3} and R^{a4} are independently selected from hydrogen, (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-; (C₁-C₆)alkoxy optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, [(C₁-C₆)alkyl]-C(=O)-, (C₁-C₆)alkoxy, [(C₁-C₆)alkoxy]-C(=O)-, R^{a5}R^{a6}N- and R^{a7}R^{a8}N-C(=O)-, wherein R^{a5}, R^{a6}, R^{a7} and R^{a8} are independently selected from hydrogen, (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-; C(=O)-[(C₁-C₆)alkyl] wherein said (C₁-C₆)alkyl is optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, [(C₁-C₆)alkyl]-C(=O)-, (C₁-C₆)alkoxy, [(C₁-C₆)alkoxy]-C(=O)-, R^{a1}R^{a2}N- and R^{a3}R^{a4}N-C(=O)-, wherein R^{a1}, R^{a2}, R^{a3} and R^{a4} are independently selected from hydrogen, (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-; C(=O)-NR^{W11}R^{W12} wherein R^{W11} and R^{W12} are independently selected from hydrogen and (C₁-C₆)alkyl optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, [(C₁-C₆)alkyl]-C(=O)-, (C₁-C₆)alkoxy, [(C₁-C₆)alkoxy]-C(=O)-, R^{a1}R^{a2}N- and R^{a3}R^{a4}N-C(=O)-, wherein R^{a1}, R^{a2}, R^{a3} and R^{a4} are independently selected from hydrogen, (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-; NR^{W13}R^{W14} wherein R^{W13} and R^{W14} are independently selected from hydrogen and (C₁-C₆)alkyl optionally substituted with

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one to three substituents independently selected from halo, hydroxy, carboxy, [(C₁-C₆)alkyl]-C(=O)-, (C₁-C₆)alkoxy, [(C₁-C₆)alkoxy]-C(=O)-, R^{a1}R^{a2}N- and R^{a3}R^{a4}N-C(=O)-, wherein R^{a1}, R^{a2}, R^{a3} and R^{a4} are independently selected from hydrogen, (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-; aryl selected from phenyl and naphthyl; and four- to eight-membered heterocyclyl containing one to four hetero atoms independently selected from nitrogen, oxygen and sulfur;

A is AE wherein

Yⁱ, Y^j, Y^k and Y^m are independently selected from C(=O); CR^{Y1}R^{Y2}; CR^{Y3}[C(=O)R^{Y4}]; CR^{Y3}[NR^{Y5}C(=O)R^{Y4}]; CR^{Y3}[C(=O)NR^{Y6}R^{Y7}]; CR^{Y3}[NR^{Y6}R^{Y7}]; O; S; SO₂; NH; N[(C₁-C₆)alkyl] wherein said (C₁-C₆)alkyl is optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, [(C₁-C₆)alkyl]-C(=O)-, (C₁-C₆)alkoxy, [(C₁-C₆)alkoxy]-C(=O)-, R^{a1}R^{a2}N- and R^{a3}R^{a4}N-C(=O)-, wherein R^{a1}, R^{a2}, R^{a3} and R^{a4} are independently selected from hydrogen, (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-; N-(CH₂)_{n3}-heterocyclyl wherein n3 is an integer selected from 0, 1, 2 and 3, and said heterocyclyl contains from four to eight ring atoms one or two of which are independently selected from nitrogen, oxygen and sulfur; N-(CH₂)_{n4}-aryl wherein n4 is an integer selected from 0, 1, 2 and 3, and said aryl is selected from phenyl and naphthyl; and N-(CH₂)_{n5}-heteroaryl wherein n5 is an integer selected from 0, 1, 2 and 3, and said heteroaryl is a five to ten membered aromatic heterocyclyl containing from one to four hetero atoms independently selected from nitrogen, oxygen and sulfur;

R^{Y1} and R^{Y2} are independently selected from hydrogen; hydroxy; non-, mono- and di-substituted amino wherein the substituents are independently selected from (C₁-C₆)alkyl; [(C₁-C₆)alkyl]-C(=O)-; [(C₁-C₆)alkoxy]-C(=O)-; [(C₁-C₆)alkyl]-SO₂-; and four- to eight-membered heterocyclyl containing one to four hetero atoms independently selected from nitrogen, oxygen and sulfur, wherein said heterocyclyl is optionally substituted with one to three substituents independently selected from hydroxy, (C₁-C₆)alkyl, NH₂-C(=O)-, [(C₁-C₆)alkyl]-NH-C(=O)-, [(C₁-C₆)alkyl]₂-N-C(=O)-, and non-, mono- and di-substituted amino wherein the substituents are independently selected from

(C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-; (C₁-C₆)alkyl optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, [(C₁-C₆)alkyl]-C(=O)-, (C₁-C₆)alkoxy, [(C₁-C₆)alkoxy]-C(=O)-, R^{a1}R^{a2}N- and R^{a3}R^{a4}N-C(=O)-, wherein R^{a1}, R^{a2}, R^{a3} and R^{a4} are independently selected from hydrogen, (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-; and (C₁-C₆)alkoxy optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, [(C₁-C₆)alkyl]-C(=O)-, (C₁-C₆)alkoxy, [(C₁-C₆)alkoxy]-C(=O)-, R^{a5}R^{a6}N- and R^{a7}R^{a8}N-C(=O)-, wherein R^{a5}, R^{a6}, R^{a7} and R^{a8} are independently selected from hydrogen, (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-; or

R^{Y1} and R^{Y2} taken together with the carbon atom to which they are attached form spiropyrrolidinyl or spiropiperidinyl, both of which are optionally N-substituted with a substituent selected from (C₁-C₆)alkyl, (C₁-C₆)alkyl-C(=O)-, [(C₁-C₆)alkyl]-C(=O)-(C₁-C₆)alkyl and aryl-(C=O)- wherein aryl is selected from phenyl and naphthyl;

R^{Y3} is hydrogen;

R^{Y4} is selected from hydroxy; (C₁-C₆)alkyl optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, [(C₁-C₆)alkyl]-C(=O)-, (C₁-C₆)alkoxy, [(C₁-C₆)alkoxy]-C(=O)-, R^{a1}R^{a2}N- and R^{a3}R^{a4}N-C(=O)-, wherein R^{a1}, R^{a2}, R^{a3} and R^{a4} are independently selected from hydrogen, (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-; and (C₁-C₆)alkoxy optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, [(C₁-C₆)alkyl]-C(=O)-, (C₁-C₆)alkoxy, [(C₁-C₆)alkoxy]-C(=O)-, R^{a5}R^{a6}N- and R^{a7}R^{a8}N-C(=O)-, wherein R^{a5}, R^{a6}, R^{a7} and R^{a8} are independently selected from hydrogen, (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-; and

R^{Y5}, R^{Y6} and R^{Y7} are independently selected from hydrogen; (C₁-C₆)alkyl optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, [(C₁-C₆)alkyl]-C(=O)-, (C₁-C₆)alkoxy, [(C₁-

C_6 alkoxy]-C(=O)-, $R^{a1}R^{a2}N$ - and $R^{a3}R^{a4}N$ -C(=O)-, wherein R^{a1} , R^{a2} , R^{a3} and R^{a4} are independently selected from hydrogen, (C_1-C_6) alkyl, $[(C_1-C_6)alkyl]-C(=O)-$, $[(C_1-C_6)alkoxy]-C(=O)-$ and $[(C_1-C_6)alkyl]-SO_2-$; heterocyclyl-(CH₂)_{n6}- wherein n6 is an integer selected from 0, 1, 2, 3 and 4 and said heterocyclyl is four to eight membered containing one to three hetero atoms independently selected from nitrogen, oxygen and sulfur, wherein said heterocyclyl is optionally substituted with one to three substituents independently selected from hydroxy; (C_1-C_6) alkyl; $NH_2-C(=O)-$; $(C_1-C_6)alkyl-NH-C(=O)-$; $[(C_1-C_6)alkyl]_2-N-C(=O)-$; and non-, mono- and di-substituted amino wherein the substituents are independently selected from $(C_1-C_6)alkyl$, $[(C_1-C_6)alkyl]-C(=O)-$, $[(C_1-C_6)alkoxy]-C(=O)-$ and $[(C_1-C_6)alkyl]-SO_2-$; and heteroaryl-(CH₂)_{n7}- wherein n7 is an integer selected from 0, 1, 2, 3 and 4 and said heteroaryl is five to ten membered containing one to three hetero atoms independently selected from nitrogen, oxygen and sulfur, wherein said heteroaryl is optionally substituted with one to three substituents independently selected from hydroxy; $(C_1-C_6)alkyl$; $NH_2-C(=O)-$; $(C_1-C_6)alkyl-NH-C(=O)-$; $[(C_1-C_6)alkyl]_2-N-C(=O)-$; and non-, mono- and di-substituted amino wherein the substituents are independently selected from $(C_1-C_6)alkyl$, $[(C_1-C_6)alkyl]-C(=O)-$, $[(C_1-C_6)alkoxy]-C(=O)-$ and $[(C_1-C_6)alkyl]-SO_2-$; or

R^{Y6} and R^{Y7} taken together with the nitrogen atom to which they are attached form a four to eight heterocyclyl optionally containing, in addition to the nitrogen atom, one to two additional hetero atoms independently selected from nitrogen, oxygen and sulfur, and said heterocyclyl is optionally substituted with one substituent selected from hydroxy; $(C_1-C_6)alkyl$; $NH_2-C(=O)-$; $(C_1-C_6)alkyl-NH-C(=O)-$; $[(C_1-C_6)alkyl]_2-N-C(=O)-$; and non-, mono- and di-substituted amino wherein the substituents are independently selected from $(C_1-C_6)alkyl$, $[(C_1-C_6)alkyl]-C(=O)-$, $[(C_1-C_6)alkoxy]-C(=O)-$ and $[(C_1-C_6)alkyl]-SO_2-$; and

said A is optionally substituted in the fused benzene rings with one to four substituents independently selected from halo; hydroxy; mercapto; phenyl; $(C_1-C_6)alkyl$ optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, $[(C_1-C_6)alkyl]-C(=O)-$, $(C_1-C_6)alkoxy$, $[(C_1-C_6)alkoxy]-C(=O)-$, $R^{a1}R^{a2}N$ - and

$R^{a3}R^{a4}N-C(=O)-$, wherein R^{a1} , R^{a2} , R^{a3} and R^{a4} are independently selected from hydrogen, $(C_1-C_6)alkyl$, $[(C_1-C_6)alkyl]-C(=O)-$, $[(C_1-C_6)alkoxy]-C(=O)-$ and $[(C_1-C_6)alkyl]-SO_2-$; and $(C_1-C_6)alkoxy$ optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, $[(C_1-C_6)alkyl]-C(=O)-$, $(C_1-C_6)alkoxy$, $[(C_1-C_6)alkoxy]-C(=O)-$, $R^{a5}R^{a6}N-$ and $R^{a7}R^{a8}N-C(=O)-$, wherein R^{a5} , R^{a6} , R^{a7} and R^{a8} are independently selected from hydrogen, $(C_1-C_6)alkyl$, $[(C_1-C_6)alkyl]-C(=O)-$, $[(C_1-C_6)alkoxy]-C(=O)-$ and $[(C_1-C_6)alkyl]-SO_2-$; and
 Z is selected from $C(=O)$; $(CH_2)_{n8}$ wherein $n8$ is an integer selected from 0, 1 and 2;

and

10 CHR^{Z1} wherein

R^{Z1} is selected from carboxy; $(C_1-C_6)alkoxy-C(=O)-$; non-, mono- and di-substituted amino wherein the substituents are independently selected from $(C_1-C_6)alkyl$, $[(C_1-C_6)alkyl]-C(=O)-$, $[(C_1-C_6)alkyl]-C(=O)-O-$ and $[(C_1-C_6)alkyl]-SO_2-$; $(C_1-C_6)alkyl$ optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, $[(C_1-C_6)alkyl]-C(=O)-$, $(C_1-C_6)alkoxy$, $[(C_1-C_6)alkoxy]-C(=O)-$, $R^{a1}R^{a2}N-$ and $R^{a3}R^{a4}N-C(=O)-$, wherein R^{a1} , R^{a2} , R^{a3} and R^{a4} are independently selected from hydrogen, $(C_1-C_6)alkyl$, $[(C_1-C_6)alkyl]-C(=O)-$, $[(C_1-C_6)alkoxy]-C(=O)-$ and $[(C_1-C_6)alkyl]-SO_2-$; and $[C(=O)-NR^{Z11}R^{Z12}]$ wherein R^{Z11} and R^{Z12} are independently selected from hydrogen and $(C_1-C_6)alkyl$ optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, $[(C_1-C_6)alkyl]-C(=O)-$, $(C_1-C_6)alkoxy$, $[(C_1-C_6)alkoxy]-C(=O)-$, $R^{a1}R^{a2}N-$ and $R^{a3}R^{a4}N-C(=O)-$, wherein R^{a1} , R^{a2} , R^{a3} and R^{a4} are independently selected from hydrogen, $(C_1-C_6)alkyl$, $[(C_1-C_6)alkyl]-C(=O)-$, $[(C_1-C_6)alkoxy]-C(=O)-$ and $[(C_1-C_6)alkyl]-SO_2-$.

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10. A compound according to Claim 1 wherein

all R^1 are hydrogen

each R^2 is independently selected from hydrogen and halo;

X^1 and X^2 are independently selected from the group consisting of $C[(C_1-C_6)alkyl]$ and $C-OH$;

30

W^1 and W^2 are both CH_2 ;

A is AB wherein

Y^b is selected from $C(=O)$; $CR^{Y1}R^{Y2}$; $CR^{Y3}[C(=O)R^{Y4}]$; $CR^{Y3}[NR^{Y5}C(=O)R^{Y4}]$; $CR^{Y3}[C(=O)NR^{Y6}R^{Y7}]$; and $CR^{Y3}[NR^{Y6}R^{Y7}]$;

Y^c is selected from O; S; SO_2 ; NH; $N[(C_1-C_6)alkyl]$ wherein said $(C_1-C_6)alkyl$ is optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, $[(C_1-C_6)alkyl]-C(=O)-$, $(C_1-C_6)alkoxy$, $[(C_1-C_6)alkoxy]-C(=O)-$, $R^{a1}R^{a2}N-$ and $R^{a3}R^{a4}N-C(=O)-$, wherein R^{a1} , R^{a2} , R^{a3} and R^{a4} are independently selected from hydrogen, $(C_1-C_6)alkyl$, $[(C_1-C_6)alkyl]-C(=O)-$, $[(C_1-C_6)alkoxy]-C(=O)-$ and $[(C_1-C_6)alkyl]-SO_2-$; $N-(CH_2)_{n3}$ -heterocyclyl wherein $n3$ is an integer selected from 0, 1, 2 and 3, and said heterocyclyl contains from four to eight ring atoms one or two of which are independently selected from nitrogen, oxygen and sulfur; $N-(CH_2)_{n4}$ -aryl wherein $n4$ is an integer selected from 0, 1, 2 and 3, and said aryl is selected from phenyl and naphthyl; and $N-(CH_2)_{n5}$ -heteroaryl wherein $n5$ is an integer selected from 0, 1, 2 and 3, and said heteroaryl is a five to ten membered aromatic heterocyclyl containing from one to four hetero atoms independently selected from nitrogen, oxygen and sulfur; wherein

R^{Y1} and R^{Y2} are independently selected from hydrogen; hydroxy; non-, mono- and di-substituted amino wherein the substituents are independently selected from $(C_1-C_6)alkyl$; $[(C_1-C_6)alkyl]-C(=O)-$; $[(C_1-C_6)alkoxy]-C(=O)-$; $[(C_1-C_6)alkyl]-SO_2-$; and four- to eight-membered heterocyclyl containing one to four hetero atoms independently selected from nitrogen, oxygen and sulfur, wherein said heterocyclyl is optionally substituted with one to three substituents independently selected from hydroxy, $(C_1-C_6)alkyl$, $NH_2-C(=O)-$, $[(C_1-C_6)alkyl]-NH-C(=O)-$, $[(C_1-C_6)alkyl]_2-N-C(=O)-$, and non-, mono- and di-substituted amino wherein the substituents are independently selected from $(C_1-C_6)alkyl$, $[(C_1-C_6)alkyl]-C(=O)-$, $[(C_1-C_6)alkoxy]-C(=O)-$ and $[(C_1-C_6)alkyl]-SO_2-$; $(C_1-C_6)alkyl$ optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, $[(C_1-C_6)alkyl]-C(=O)-$, $(C_1-C_6)alkoxy$, $[(C_1-C_6)alkoxy]-C(=O)-$, $R^{a1}R^{a2}N-$ and $R^{a3}R^{a4}N-C(=O)-$, wherein R^{a1} , R^{a2} , R^{a3} and R^{a4} are independently selected from hydrogen, $(C_1-C_6)alkyl$, $[(C_1-C_6)alkyl]-C(=O)-$, $[(C_1-C_6)alkoxy]-C(=O)-$ and $[(C_1-C_6)alkyl]-SO_2-$; and $(C_1-C_6)alkoxy$ optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, $[(C_1-$

C₆)alkyl]-C(=O)-, (C₁-C₆)alkoxy, [(C₁-C₆)alkoxy]-C(=O)-, R^{a5}R^{a6}N- and R^{a7}R^{a8}N-C(=O)-, wherein R^{a5}, R^{a6}, R^{a7} and R^{a8} are independently selected from hydrogen, (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-; or

5 R^{Y1} and R^{Y2} taken together with the carbon atom to which they are attached form spiropyrrolidiny1 or spiropiperidiny1, both of which are optionally N-substituted with a substituent selected from (C₁-C₆)alkyl, (C₁-C₆)alkyl-C(=O)-, [(C₁-C₆)alkyl]-C(=O)-(C₁-C₆)alkyl and aryl-(C=O)- wherein aryl is selected from phenyl and naphthyl;

10 R^{Y3} is hydrogen;

R^{Y4} is selected from hydroxy; (C₁-C₆)alkyl optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, [(C₁-C₆)alkyl]-C(=O)-, (C₁-C₆)alkoxy, [(C₁-C₆)alkoxy]-C(=O)-, R^{a1}R^{a2}N- and R^{a3}R^{a4}N-C(=O)-, wherein R^{a1}, R^{a2}, R^{a3} and R^{a4} are independently selected from
15 hydrogen, (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-; and (C₁-C₆)alkoxy optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, [(C₁-C₆)alkyl]-C(=O)-, (C₁-C₆)alkoxy, [(C₁-C₆)alkoxy]-C(=O)-, R^{a5}R^{a6}N- and R^{a7}R^{a8}N-C(=O)-, wherein R^{a5}, R^{a6}, R^{a7} and R^{a8} are independently selected from
20 hydrogen, (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-; and

R^{Y5}, R^{Y6} and R^{Y7} are independently selected from hydrogen; (C₁-C₆)alkyl optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, [(C₁-C₆)alkyl]-C(=O)-, (C₁-C₆)alkoxy, [(C₁-C₆)alkoxy]-C(=O)-, R^{a1}R^{a2}N- and R^{a3}R^{a4}N-C(=O)-, wherein R^{a1}, R^{a2}, R^{a3} and R^{a4}
25 are independently selected from hydrogen, (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-; heterocyclyl-(CH₂)_{n6}- wherein n₆ is an integer selected from 0, 1, 2, 3 and 4 and said heterocyclyl is four to eight membered containing one to three hetero atoms independently selected
30 from nitrogen, oxygen and sulfur, wherein said heterocyclyl is optionally substituted with one to three substituents independently selected from hydroxy; (C₁-C₆)alkyl; NH₂-C(O=)-; (C₁-C₆)alkyl-NH-C(=O)-; [(C₁-C₆)alkyl]₂-N-C(=O)-

5 ; and non-, mono- and di-substituted amino wherein the substituents are independently selected from (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-; and heteroaryl-(CH₂)_{n7}- wherein n7 is an integer selected from 0, 1, 2, 3 and 4 and said heteroaryl is five to ten membered containing one to three hetero atoms independently selected from nitrogen, oxygen and sulfur, wherein said heteroaryl is optionally substituted with one to three substituents independently selected from hydroxy; (C₁-C₆)alkyl; NH₂-C(=O)-; (C₁-C₆)alkyl-NH-C(=O)-; [(C₁-C₆)alkyl]₂-N-C(=O)-; and non-, mono- and di-substituted amino wherein the substituents are independently selected from (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-; or

10 R^{Y6} and R^{Y7} taken together with the nitrogen atom to which they are attached form a four to eight heterocyclyl optionally containing, in addition to the nitrogen atom, one to two additional hetero atoms independently selected from nitrogen, oxygen and sulfur, and said heterocyclyl is optionally substituted with one substituent selected from hydroxy; (C₁-C₆)alkyl; NH₂-C(=O)-; (C₁-C₆)alkyl-NH-C(=O)-; [(C₁-C₆)alkyl]₂-N-C(=O)-; and non-, mono- and di-substituted amino wherein the substituents are independently selected from (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-;

15 said A is optionally substituted in the fused benzene rings with one to four substituents independently selected from halo; hydroxy; mercapto; phenyl; (C₁-C₆)alkyl optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, [(C₁-C₆)alkyl]-C(=O)-, (C₁-C₆)alkoxy, [(C₁-C₆)alkoxy]-C(=O)-, R^{a1}R^{a2}N- and R^{a3}R^{a4}N-C(=O)-, wherein R^{a1}, R^{a2}, R^{a3} and R^{a4} are independently selected from hydrogen, (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-; and (C₁-C₆)alkoxy optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, [(C₁-C₆)alkyl]-C(=O)-, (C₁-C₆)alkoxy, [(C₁-C₆)alkoxy]-C(=O)-, R^{a5}R^{a6}N- and R^{a7}R^{a8}N-C(=O)-, wherein R^{a5}, R^{a6}, R^{a7} and R^{a8} are independently selected from hydrogen, (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-; and

20 Z is selected from C(=O); (CH₂)_{n8} wherein n8 is an integer selected from 0, 1 and 2;

and

CHR^{Z1} wherein

R^{Z1} is selected from carboxy; (C₁-C₆)alkoxy-C(=O)-; non-, mono- and di-substituted amino wherein the substituents are independently selected from (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkyl]-C(=O)-O- and [(C₁-C₆)alkyl]-SO₂-; (C₁-C₆)alkyl optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, [(C₁-C₆)alkyl]-C(=O)-, (C₁-C₆)alkoxy, [(C₁-C₆)alkoxy]-C(=O)-, R^{a1}R^{a2}N- and R^{a3}R^{a4}N-C(=O)-, wherein R^{a1}, R^{a2}, R^{a3} and R^{a4} are independently selected from hydrogen, (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-; and [C(=O)-NR^{Z11}R^{Z12}] wherein R^{Z11} and R^{Z12} are independently selected from hydrogen and (C₁-C₆)alkyl optionally substituted with one to three substituents independently selected from halo, hydroxy, carboxy, [(C₁-C₆)alkyl]-C(=O)-, (C₁-C₆)alkoxy, [(C₁-C₆)alkoxy]-C(=O)-, R^{a1}R^{a2}N- and R^{a3}R^{a4}N-C(=O)-, wherein R^{a1}, R^{a2}, R^{a3} and R^{a4} are independently selected from hydrogen, (C₁-C₆)alkyl, [(C₁-C₆)alkyl]-C(=O)-, [(C₁-C₆)alkoxy]-C(=O)- and [(C₁-C₆)alkyl]-SO₂-.

11. A compound according to Claim 1 selected from
 - 2,3-dihydro-1'-{3-[2-(*N*-methylaminocarbonyl)indolin-1-yl]-3-oxopropyl}spiro[1*H*-indene-1,4'-piperidine];
 - 2,3-dihydro-1'-[3-(2-*N,N*-dimethylaminocarbonylindolin-1-yl)-3-oxopropyl]spiro[1*H*-indene-1,4'-piperidine];
 - 2,3-dihydro-1'-[3-(2-morpholinocarbonylindolin-1-yl)-3-oxopropyl]spiro[1*H*-indene-1,4'-piperidine];
 - 2,3-dihydro-1'-[3-(2-carbamoylindolin-1-yl)-3-oxopropyl]spiro[1*H*-indene-1,4'-piperidine] hydrochloride;
 - 2,3-dihydro-1'-{3-[2-(1-ethylpyrrolidin-3-yl)aminocarbonylindolin-1-yl]-3-oxopropyl}spiro[1*H*-indene-1,4'-piperidine];
 - 2,3-dihydro-1'-{3-[2-(*S*)-(N,N-dimethylaminoethyl)aminocarbonylindolin-1-yl]-3-oxopropyl}spiro[1*H*-indene-1,4'-piperidine];
 - 2,3-dihydro-1'-{3-[2-(*S*)-(2-hydroxyethyl)aminocarbonylindolin-1-yl]-3-oxopropyl}spiro[1*H*-indene-1,4'-piperidine];

- 2,3-dihydro-1'-{3-[2-(S)-(2-aminoethyl)aminocarbonylindolin-1-yl]-3-oxopropyl}spiro[1*H*-indene-1,4'-piperidine];
- 2,3-dihydro-1'-{3-[2-(S)-(2-acetamidoethyl)aminocarbonylindolin-1-yl]-3-oxopropyl}spiro[1*H*-indene-1,4'-piperidine];
- 5 2,3-dihydro-1'-{3-[2-(S)-(2-methanesulfonamidoethyl)aminocarbonylindolin-1-yl]-3-oxopropyl}spiro[1*H*-indene-1,4'-piperidine];
- 2,3-dihydro-1'-[3-(2-(S)-*N*-methylaminocarbonylindolin-1-yl)-3-oxopropyl]spiro[1*H*-indene-1,4'-piperidine];
- 2,3-dihydro-1'-[3-(2-(S)-*N,N*-dimethylaminocarbonylindolin-1-yl)-3-oxopropyl]spiro[1*H*-indene-1,4'-piperidine];
- 10 2,3-dihydro-1'-{3-[2-(S)-(4-morpholinecarbonyl)indolin-1-yl]-3-oxopropyl}spiro[1*H*-indene-1,4'-piperidine];
- 2,3-dihydro-1'-[3-(2-(S)-aminocarbonylindolin-1-yl)-3-oxopropyl]spiro[1*H*-indene-1,4'-piperidine];
- 15 2,3-dihydro-1'-[3-(2-methoxycarbonylindolin-1-yl)-3-oxopropyl]spiro[1*H*-indene-1,4'-piperidine];
- 2,3-dihydro-1'-[3-(indolin-1-yl)-3-oxopropyl]spiro[1*H*-indene-1,4'-piperidine];
- 2,3-dihydro-1'-[3-(2-(S)-methoxycarbonylindolin-1-yl)-3-oxopropyl]spiro[1*H*-indene-1,4'-piperidine];
- 20 2,3-dihydro-1'-indolyl-3-oxopropylspiro[1*H*-indene-1,4'-piperidine];
- 2,3-dihydro-1'-[3-(2-hydroxymethylindolin-1-yl)-3-oxopropyl]spiro[1*H*-indene-1,4'-piperidine];
- 2,3-dihydro-1'-[3-(2-methoxymethylindolin-1-yl)-3-oxopropyl]spiro[1*H*-indene-1,4'-piperidine];
- 25 2,3-dihydro-1'-[3-(benzimidazol-2-one-1-yl)propyl]spiro[1*H*-indene-1,4'-piperidine];
- 2,3-dihydro-1'-[3-(benzothiazol-2-one-1-yl)propyl]spiro[1*H*-indene-1,4'-piperidine];
- 2,3-dihydro-1'-[3-(2-oxo-1,3-benzoxazol-3(2*H*)-yl)propyl]spiro[1*H*-indene-1,4'-piperidine];
- 2,3-dihydro-1'-[3-(2-hydroxymethylbenzimidazol-1-yl)-3-oxopropyl]spiro[1*H*-indene-1,4'-piperidine];
- 30 1,4'-piperidine];
- 2,3-dihydro-1'-[3-(3-ethylbenzimidazol-2-one-1-yl)propyl]spiro[1*H*-indene-1,4'-piperidine];

2,3-dihydro-1'-[3-(2-acetamidobenzimidazol-1-yl)propyl]spiro[1*H*-indene-1,4'-piperidine];

2,3-dihydro-1'-{3-[3-(2-hydroxyethyl)benzimidazol-2-one-1-yl)propyl]spiro[1*H*-indene-1,4'-piperidine];

5 2,3-dihydro-1'-{3-[3-(2-aminoethyl)benzimidazol-2-one-1-yl)propyl]spiro[1*H*-indene-1,4'-piperidine];

2,3-dihydro-1'-{3-[3-(2-acetamidoethyl)benzimidazol-2-one-1-yl)propyl]spiro[1*H*-indene-1,4'-piperidine];

10 2,3-dihydro-1'-[3-(2-oxo-3,4-dihydro-1(2*H*)-quinoliny]propyl]spiro[1*H*-indene-1,4'-piperidine];

2,3-dihydro-1'-[3-(3-methyl-2-oxo-3,4-dihydro-1(2*H*)-quinazoliny]propyl]spiro[1*H*-indene-1,4'-piperidine];

2,3-dihydro-1'-[3-oxo-3-(2,3,4,5-tetrahydro-1*H*-benzazepin-1-yl)propyl]spiro[1*H*-indene-1,4'-piperidine];

15 1'-[3-[(2*S*)-2-[(dimethylamino)carbonyl]-2,3-dihydro-1*H*-indol-1-yl]-3-oxopropyl]spiro[(2-hydroxy)indane-1,4'-piperidine]; and

1'-[3-[(2*S*)-2-[(dimethylamino)carbonyl]-2,3-dihydro-1*H*-indol-1-yl]-3-oxopropyl]spiro[(3-methyl)indane-1,4'-piperidine] or a salt thereof.

20 12. A pharmaceutical composition comprising an effective amount of a compound of claim 1 and a pharmaceutically acceptable carrier for treating a disease or medical condition mediated by ORL1-receptor and its endogenous ligand in a mammal including a human.

25 13. A method for treating or preventing a disease or condition in a mammal including a human, which disease or condition is mediated by ORL-1 receptor and its endogenous ligand, comprising administering an effective amount of a compound of Claim 1 to a mammal including a human, which suffered from such disease or condition.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/IB 02/02272

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D401/06 C07D417/06 C07D413/06 C07D401/14 C07D471/10
C07D491/10 C07D513/14 A61P25/04 A61K31/435 A61K31/495
A61K31/535 A61K31/55

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 02 26714 A (ARAI TOSHIMITSU ;KAMIYAMA KEIJI (JP); NISHIKIMI YUJI (JP); IMAMURA) 4 April 2002 (2002-04-04) page 53, examples 9-11; page 63, examples 12-21; ---	1-11
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Y	US 3 979 513 A (GALT RONALD HILSON BEGG ET AL) 7 September 1976 (1976-09-07) claims 1,9 ---	1-13
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☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
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- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- * & * document member of the same patent family

Date of the actual completion of the international search

22 August 2002

Date of mailing of the International search report

02/09/2002

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INTERNATIONAL SEARCH REPORT

International Application No

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB 02/02272

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claim 13 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte I Application No
PCT/IB 02/02272

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International Application No

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